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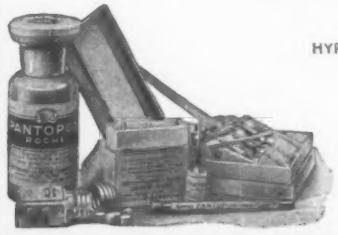

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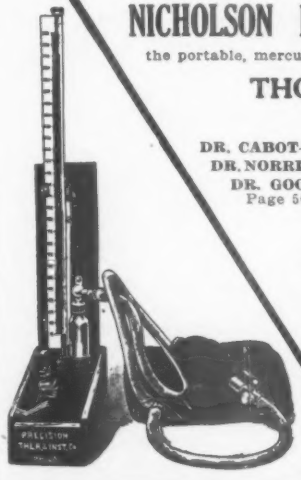

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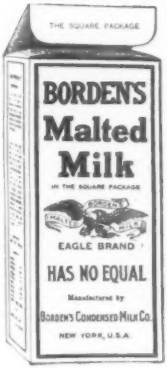

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ORIGINAL ARTICLES

THE ETIOLOGY OF SPRUE.

By Bailey K. Ashford, M.D., Sc.D.,

LIEUTENANT-COLONEL, U. S. ARMY; PRESIDENT OF A BOARD FOR THE STUDY OF TROPICAL DISEASES AS THEY EXIST IN PORTO RICO.

(From the Institute of Tropical Medicine and Hygiene of Porto Rico.)

The object of this paper is to demonstrate that the species of Monilia first described by me in March, 1915[1] is the determining etiological factor in sprue, and to suggest that this species be recognized as Monilia psilosis, Ashford, 1914.

It was stated in a paper presented by the writer May 13, 1915, before the annual meeting of the Association of American Physicians,[2] that Dr. Isaac Gonzalez, member of the Institute of Tropical Medicine and Hygiene of Porto Rico, working with an antigen prepared from three strains of this species furnished him by me, had demonstrated in 4 cases of sprue a deviation of the complement, and that in 12 cases not sprue no such deviation could be obtained. The consensus of opinion expressed individually after that meeting was that until the demonstration of a reaction specific to this particular organism should be forthcoming the results should be considered to be due to a group reaction, thus withholding the decision as to the relation of my organism to sprue, although all other evidence, clinical, epidemiological, and mycological, as well as animal experimentation, spoke strongly for its specificity.

[1] A Monilia Found in Certain Cases of Sprue, Preliminary Note, Jour. Am. Med. Assn., March 6, 1915, lxiv, 810–811.

[2] Studies in Moniliasis of the Digestive Tract in Porto Rico, Am. Jour. Med. Sc., 1915, No. 5, cl, 680.

For the solution of this problem, after six months' more preliminary work, I determined to make a study of a series of 100 persons, some of whom were clinically free from sprue, some typical cases of the disease, and some whose clinical picture did not permit of a positive diagnosis, considering, however, as sprue only such cases as should prove themselves positive, clinically, mycologically, and serologically. Only very slight and justifiable departures have been made from this plan, as will be seen later.

The interpretation of the deviation of the complement, as is well known, is not only a matter into which the personal equation enters, but such highly specialized laboratory work requires long

FIG. 1.—Non-specific commensal from a case of pellagra. Case CCXXIa. Note short articles, heavily nucleated and granular yeasts and large size of the elements. (Photograph made in the Institute of Tropical Medicine and Hygiene of Porto Rico.)

experience, careful technic, and, in short, genuine ability. It was evident that such reactions should be made by some such person who should have no knowledge whatever of the clinical and mycological history of the case, and who would simply receive the blood of the patient without any inkling of such history, without even seeing the patient. Dr. Gonzalez Martinez, whose previous work has been mentioned above, was on a visit to the North, and the uncertainty of my being able to continue this research without interruption was very great. I was fortunate enough to associate myself in the study of this series with Dr. Carl Michel, of the U. S. Public Health Service, recently assigned to duty for his service in San Juan, and now a collaborator in this institute. This serologist

had spent a long time, previous to his arrival here, in doing this very kind of blood work in syphilis and experimentally in other diseases, and was peculiarly prepared by his experience to fill all of the requisites desired. The results, of course, have been recorded as received from him and incorporated with the clinical and mycological history of each case. His own report appears elsewhere in this JOURNAL, and his technic and conclusions are expressed individually.

So while there has been a great effort made to elucidate the facts in this series, there has been no straining after-effect nor any divergence from the avowed intention to let these facts speak for themselves.

FIG. 2.—Wild yeast found in feces. Case CLXXVIb². (Photograph made in the Institute of Tropical Medicine and Hygiene of Porto Rico.)

The work has been, as can be imagined, a very arduous one. Not only was it necessary to obtain a clear history in which neither patient nor physician would unconsciously accentuate important symptoms, but a thorough mycological study of the tongue-scrapings and feces was exacted in each case. This latter work was most time-consuming, as plate cultures had to be made of all Monilia-like colonies, and as frequently more than one species was found, and each had to be plated out and run through the proof media, several hundred such cultures were necessary.

With two or three exceptions all of the series were personal cases of the writer, and were seen by him and treated day by day, week by week, thus adding the control of the clinician to the laboratory findings.

The routine observed was as follows: After the clinical history had been taken, cultures from scrapings of the tongue on glucose agar slants and streak cultures from the feces in glucose-agar plates were made. Suspicious colonies were plated out for pure culture on a 4 per cent. glucose-agar (Sabouraud), + 2 acidity. These plates were incubated for from three to five days. At about the same time a technician of this laboratory, Mr. Jose Loubriel, secured 5 c.c. of blood from a vein of the arm, the blood tube was given a key designation, and it was delivered to Dr. Michel for serological examination after previous centrifugalization and decomplementation. The plate cultures were now examined with a hand

FIG. 3.—Yeasts and hyphæ, Monilia psilosis. Case CCXXXIIIb. (Photograph made in the Institute of Tropical Medicine and Hygiene of Porto Rico.)

glass and all Monilia-suspicious colonies were fished. This process is an important one and taxes the skill of the operator, as fine differences in color, consistency, and polish of the surface make for success. The selection of the right creamy colony when small is most difficult, and often impossible. Only after repeated plating of feces in quiescent cases of sprue was it possible to demonstrate Monilia psilosis, and in some, as will be seen, they have not yet been isolated, due to the fact that the wrong colony has been fished or that the surface yeast production in the infected intestinal canal is insufficient to give colonies in a limited number of plates. It is well known that in the quiescent stage of sprue, where neither tongue nor intestine is acutely inflamed, only the past history and present

cachexia remain to justify a probable diagnosis. It has been suggested by the writer that in such cases the mycelial elements lie latent in the submucosa awaiting a favorable opportunity to bud and spread yeasts over the surface. In such cases a serological examination will demonstrate a positive reaction, generally weak, and yet only persistent effort will reveal a chance colony. Of course, it is possible that the group reaction, of which I will later speak, is responsible for the serological result, but that this is unlikely is evident from all of the overwhelming evidence presented heretofore, in previous papers, and especially from the fact that time and again repeated work reveals a stray colony of Monilia psilosis after several

FIG. 4.—Young cultures of Monilia psilosis showing typical yeasts before internal structures are characteristic. Case CCXXXIIIb. (Photograph made in the Institute of Tropical Medicine and Hygiene of Porto Rico.)

failures in a case giving from the first a positive serological result. Cases 10, 42, 62, 77, 97, 98 and 99 are included in this series in order to be perfectly consistent, but I consider them incomplete until future search fails to reveal the organism. Even then the possibility that antibodies remain in the blood after disappearance of Monilia psilosis is to be considered. It should be noted, however, that 4 of these patients were cured two years ago and that their serological reaction is made now for the first time; also, that all save the last 3 have only a weak positive deviation of 25 per cent. or less. When to all of this is added the fact that antigens of other species have been used side by side with an antigen prepared from Monilia psilosis, with generally a negative, rarely a faintly positive

reaction, the group reaction, if present, must be considered of little importance in obscuring a diagnosis when a strongly positive reaction is obtained with Monilia psilosis.

Four or five days should be allowed for the development of Monilia colonies of sufficient size to permit even a guess at the species. Thus about ten days are required to acquire a pure culture. In each case all Monilia-suspicious colonies were planted separately and given a designating letter under the case number, the custom

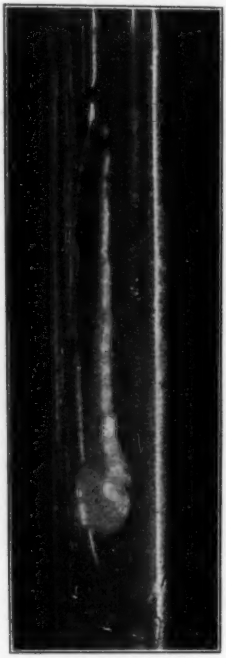

FIG. 5.—Sabouraud agar slant. Typical culture seven days Monilia psilosis. Case CLIX. (Photograph made in the Institute of Tropical Medicine and Hygiene of Porto Rico.)

of examining the cultures previously under the high-power lens being observed in order to avoid sowing bacteria. After two days more the pure culture with its number and designating letter was sown in each of the following media:

Glucose bouillon, 4 per cent., plus 2, in U-fermentation tubes
Levulose " " " " "
Maltose " " " " "
Saccharose " " " " "
Litmus milk
Plain gelatin
Sabouraud agar slants, 4 per cent. glucose, plus 2.

All save the gelatin stabs were incubated at 32 C. As soon as a U-tube showed fermentation the percentage of gas in the blind arm was read and the media was titrated against a sterile control to determine the gain or loss in acidity by the method recommended by the Bacteriological Committee of the American Public Health Association. The special value of this morphological study of cultures sown in each of four distinct sugar media was that one failed to remember, and, by the special method of recording, failed to see what the appreciation had been in the other three, which were

FIG. 6.—Sabouraud agar slant. Old culture Monilia psilosis. Case II. (Photograph made in the Institute of Tropical Medicine and Hygiene of Porto Rico.)

generally made along with many others on different days. Hence, when the note "typical" was found under all four media in the final grouping of reactions the check had been made on the personal equation of the mycologist's appreciation of form, etc.

All cultures in U-tubes failing to ferment were allowed to run fourteen days, at which time they were microscopically examined and titrated as above. The reaction in litmus milk was appreciated after fourteen days by comparing the sown tube with a control. An assistant covered the number of the culture with his hand and the color test was made by myself without knowing which was the

control and which the culture. Gelatin stabs were also allowed to run fourteen days before recording results. The gross appearance of the growth on Sabouraud agar slants was recorded after seven days and again in two weeks or more.

Bearing this unvarying technic in mind, let us consider the characteristics of Monilia psilosis:

MONILIA PSILOSIS, ASHFORD, 1914. This organism has been described by me in the two articles to which I have made reference at the beginning of this paper, but although no correction need be made of this original description some amplification must be made after several thousand more examinations.

FIG. 7.—Sabouraud agar slant. Aging three weeks Monilia psilosis. Case CXXIXb. (Photograph made in the Institute of Tropical Medicine and Hygiene of Porto Rico.)

Morphology. Only after long and careful experience does the full importance of the morphology of Monilia become impressed on the mind. For a full year the writer was confused by the variability of form and size of the elements in even a single mount from a pure culture. Monilia psilosis is a large, round, bright, clean-cut yeast, from 4 to 7 micra in diameter, with at most a few granules and a nucleus. There is also usually a pale vacuole in which a

violently motile bacillus-like body darts about. The contour is always extremely sharp and well-defined, and this contour becomes a shell-like envelope in older yeasts, often thick at one pole, for then the yeast is apt to become oval. This gives it a true signet-ring appearance. The common variations are those of size, multiplication of the nucleus, and increase in the number of the motile bodies, which are then found elsewhere than in the pale vacuole. But it should always be remembered that Monilia psilosis is not typically a granular yeast.

FIG. 8.—Gelatin stab Monilia psilosis. Case LXXVI. (Photograph made in the Institute of Tropical Medicine and Hygiene of Porto Rico.)

With this type before us we must be prepared to consider the innumerable variations always present. Reproduction by gemmation throws off great numbers of smaller yeasts, as yet imperfect in development and consequently free from the above-described internal structure, at least as far as an ordinary examination will reveal. In fact, young cultures are apt to show large round yeasts bereft of any such structure. Intermingled with these yeasts are blunt ovals which under the hanging-drop often become hyphæ. It is quite noteworthy that small nuclei and infrequent nucleation are apparently signs of a degraded type, and the patient frequently shows good resistance. Large nuclei and a tendency to mycelial

formation speak for virulent cultures. The degraded and involution forms furnish the true element of doubt in diagnosis by morphology. A degraded type can be and has been reinvested by me with all of its morphological characteristics of virulence by passage through guinea-pigs hypodermically.

If these characteristics be borne in mind the diagnosis of Monilia psilosis will not be so frequently made and carriers of wild yeasts or harmless commensals be heralded as carriers of sprue.

FIG. 9.—Gelatin stab harmless commensal. Case XL. Note short fringe. (Photograph made in the Institute of Tropical Medicine and Hygiene of Porto Rico.)

Monilia psilosis always produces mycelial elements. There are many strains in which in glucose these elements are not easily demonstrated, but the crucial test is the gelatin stab. Without the inverted pine tree in gelatin I have never permitted myself to call a Monilia, Monilia psilosis. The articles of a hypha are clear-cut, bright, and not usually very granular. They are of all sizes, 2 to 5 micra wide and of all lengths, sometimes to more than 1000 micra. They contain pale vacuoles as do the yeasts, but these are molded to the shape of the article and lie in a line of compartments, giving the appearance of a bamboo pole sawed lengthwise. In addition, large and brilliant nuclei are often seen, at times forming a regular chain of beads from end to end. Budding takes place near the

extremity of the article and offers no peculiarity except that there is never a sterigma, one of the features of sporotrichum. The articles are also usually straight and not knarled, although curious involution forms are at times seen. The extremities of the article are rounded and sometimes bulge slightly. Branching is not frequent. It occurs commonly, but it is not a feature as in some species. There is a decided preponderance in some strains to short single articles otherwise characteristic. Thin structureless, presumably sterile hyphæ, are seen and sometimes granular articles interpolated in a hypha whose articles are for the most part characteristic as described above.

FIG. 10.—Yeasts of Monilia psilosis showing nuclei. Case CXLIXb. (Photograph made in the Institute of Tropical Medicine and Hygiene of Porto Rico.)

That these characteristics are of great aid to diagnosis will be seen in my detailed records, to be later published as a bulletin of the institute, in which at different dates the morphology was described for the same culture in different sugar bouillons. The clear-cut, bright, really beautiful yeast, of large size and globular form, has served to differentiate Monilia psilosis from many other perfectly distinct species. A small yeast 1½ to 3 micra in diameter is not usually Monilia psilosis. A highly granular, highly nucleated yeast should not be ordinarily confused with it. Least of all should a persistently oval yeast. Not that all of these types cannot be found

in a culture of Monilia psilosis, but they cannot be the predominating, the characteristic type.

Litmus Milk. Practically all Monilia I have isolated strike a bluer tone to litmus milk no matter what their species. It cannot be a good proof medium, but it has been religiously employed to exclude Monilia albicans, sensu stricto, Castellani. This fungus I have never yet isolated in Porto Rico, and Bahr's statement that the probable cause of sprue is Monilia albicans I cannot substantiate. In fact, Monilia albicans seems to mean very little culturally and even less morphologically, for no author at my disposal gives a clear mycological differential diagnosis between this organism and the many other species with which it is constantly confused. The only exception is Castellani, and even he neglects its morphology, as, in fact, he does for the most if not all of the species described in his and Chalmers' *Manual of Tropical Medicine.* But Castellani distinctly states that Monilia albicans coagulates and renders litmus milk acid, and that it liquefies gelatin, and these things Monilia psilosis never does.

Gelatin. Monilia psilosis and perhaps other species produce a fine, long, hair-like mycelial extension into the non-liquefied medium. The appearance has been noted as that of an inverted pine tree, and this is fairly descriptive. A Monilia which produces a short, fringe-like, even, close, brush-like extension from the line of the stab is apparently not Monilia psilosis. Much less is a stab which gives off no mycelium. The gelatin stab is a valuable adjunct to a differential diagnosis. The organism of sprue never liquefies gelatin.

Sabouraud Agar, 4 Per Cent. Glucose, Plus 2. The growth on a Sabouraud slant is daily becoming to me of more importance in identifying this species. It is typically a very faint greenish creamy, soft, elevated growth, with clearly defined borders, and, generally, a mycelial extension beneath into the medium. This greenish tinge is by no means easy to define, and the true cream color of commensals must be used to bring it out by comparison. Even more than this, Monilia psilosis itself presents, apparently, at times a true cream color, so that the color alone is not a dependable feature, but when the faint greenish tinge is seen the organism is probably Monilia psilosis, in Porto Rico. The growth, moreover, is shiny, glistening, and brilliant at times. These characteristics are best observed at the end of seven days, as after this the culture changes. Many species were isolated which were waxy, dirty gray, dull, granular, powdery, etc., and none proved to be Monilia psilosis. Some cultures were a brilliant orange, wine-red (Santo Domingo), coral red, or yellow, but all proved to be cryptococci and no mycelium in these vividly colored organisms has been demonstrated. They are not even Monilia. But there are species which must be closely related to Monilia psilosis, and which are difficult to distinguish from it. Especially is this so of a flat, brilliant white,

or cream-colored variety and of a heaped-up creamy growth, both without mycelial extension into the medium. After a week or so the cultures of Monilia psilosis vary so widely that description fails. A few of the commoner types may be briefed as follows:

1. A dirty cream, with hard, parchment-like covering.
2. A soft, dirty cream.
3. A honeycombed, muddy growth.
4. A heaped-up mass of twisted, root-like convolutions.
5. A pitted, even crater-like, dirty growth.
6. A green, honeycombed growth.

Fermentation Tests. I take this opportunity of paying a tribute to Dr. Aldo Castellani in his demand that these yeasts be always submitted to tests which will reveal the sugars they are capable of fermenting, at the same time emphasizing again his observation that we do not want to know so much what Monilia can be taught to ferment as to record what they actually do ferment when first isolated; in other words, their usual sugar-fermenting capacity under conditions in which they are found. Everyone knows what bacteria can be made to do in a changed environment, and if this is true of bacteria it is certainly true of the protein yeast. But at the same time that I recognize the value of Professor Castellani's proof media, I wish to protest against the creation of species on these fermentation tests alone, even against giving the dominant role to such tests in deciding species. Morphology is really more important in deciding species, and serological tests even more so, as Castellani himself states, for the latter qualification.

The only sugars normally fermented by Monilia psilosis are glucose, levulose, and maltose (typically, always), saccharose (often), and galactose (occasionally). I could never accept as Monilia psilosis a yeast which fails to ferment maltose, qualifying this statement, however, by adding that in case of a probably degraded yeast of this species it is permissible to try to restore its full vigor by passage through guinea-pigs. I have thus reinvested a degraded type on several occasions (case 90 only of this series), with its lost power of mycelial production, its typical morphology, and its ability to ferment maltose; but I have ten times as frequently failed to convert what I imagined must be degraded types into Monilia psilosis, not only by one but by several such passages in particular cultures. Is it that a degraded Monilia is usually unable to recover its former characteristics, having once lost them, as in the case of the duvet-forming tricophyta; or are we handling separate but nearly related species? I believe the latter to be the case as cultural departures from Monilia psilosis were rare; their characteristics were generally immutable.

Monilia psilosis follows the universal rule of all Monilia and Cryptococci found here; there is no clouding of the medium when liquid. A more or less abundant sediment collects, but save when very freshly inoculated, or when gas bubbles up from the bottom

and disturbs this sediment, the medium is clear. This organism rarely produces a pellicle. A collar it does often produce at the point of contact of the surface of the liquid with the glass tube. Gas usually forms in a few days and rapidly increases. The most rapid gas producer is glucose, then levulose, then maltose, except when saccharose is fermented, in which case this sugar yields gas even more quickly than glucose. If gas is produced after seven days it usually, although by no means always, means contamination. All of these sugar media mentioned become more acid after inoculation, as evidenced by titration with phenolphthalein and a $\frac{2}{N}^{0}$ sodium hydrate solution against a control. They usually gain from plus 1.5 to plus 5 acidity, but rarely go higher.

These are therefore the routine methods by which Monilia psilosis has been distinguished in this laboratory. Since November, 1914, to date, February 16, 1917, nearly 300 persons, most of whom were suffering from sprue, have had their tongues and feces searched for Monilia, and these Monilia have been classified by methods above described, involving about 500 pure cultures and 8000 differential cultures, of which, in the case of the sugar media, 5000 were separately examined and their morphological characteristics recorded. All of this work, save the serological tests above noted in the last 100 cases, and the final titration of the media in the same cases, has been performed by myself, and to ensure against error I have thrown every possible doubt upon my own technic, often repeating certain cultures, especially those in maltose, over and over again. As a matter of fact, in practically every culture, the differential cultures were sown twice in succession. For these reasons I feel justified in giving what would be under other circumstances judged an unseemingly decided tone to my own views on the specificity of this organism. But I am demanding mycologically only what I have required of myself before a species could be recorded in this paper as belonging to Monilia psilosis. I hope that after the demonstration of all of these details we may be able to show that such strictness is unnecessary.

It has been by no means easy to find Monilia psilosis save in cases of true sprue with active symptoms. Some of the chronic and mild cases have been and are demanding an almost impossible amount of culture work, persistence and patience. But one thing stands out clearly to all who have gone into this laboratory to study sprue. It is unusual to find Monilia psilosis in a healthy man giving no history of past intestinal disturbance suspicious of sprue, and it is very easy to find it in cases with a sore tongue and diarrhea, in which case a 100 per cent. positive serological reaction for the deviation of the complement will, as a rule, quickly reward the investigator.

Summary of a Study of One Hundred Persons Examined Clinically, Mycologically and Serologically for Sprue. Sixty-seven were suffering from or had suffered from clinical sprue,

and one was either a carrier or had mild sprue. Thirty-two were healthy or were suffering from other diseases than sprue.

In 61 of the 68 sprue cases Monilia psilosis was isolated. Of the 7 in which it was not found, 4 had been cured for at least one or two years and gave only a 50 per cent. Wassermann positive for Monilia psilosis. The other 3 were mild chronic cases, one with a + (25 per cent.) Wassermann and the other two with a + reaction. I believe that further culture from the feces of these seven would reveal in some or all Monilia psilosis, but it was desirable for many reasons to publish this study without further delay.

Seventy-one persons gave a positive deviation of the complement with an antigen of Monilia psilosis, all but one of the cases of clinical sprue and 4 not sprue. One of the 4 included as not sprue was a case of pellagra in whom sprue may be fairly suspected as a complication from the history; this case gave a + Wasserman reaction. The others were as follows: one a case of nervous dyspepsia with a negative Wassermann using the antigen as first prepared from case 4 but with a positive, 25 per cent. using an antigen prepared from the alcoholic extract of the same strain; one a case of bacillary enterocolitis with a + Wassermann and Noguchi (2 per cent. and 10 per cent. respectively); and one of a healthy boy with an ulcer of the leg giving a Wassermann negative and a + Noguchi.

These reactions were classified both by a percentage scale and by the familiar plus signs, using four pluses, however, to indicate a complete absence of hemolysis, each plus having a value of 25 per cent. Of the 68 cases of clinical sprue: 8 gave a ∓; 13 a +; 15 a ++; 11 a +++; and 20 a ++++. Only one was negative, a girl treated by me for sprue two years ago, in whom Monilia psilosis was then easily found. At the time of the serological examination just made I failed to find Monilia psilosis in scrapings from the tongue and cultures from the feces, and she was fleshy, had a good color was apparently entirely cured. In this connection it is of interest to classify these cases further with regard to their condition *at the time of the serological test.* As is well recognized, sprue is a chronic disease with acute exacerbations—now of the tongue, now of the intestine, at times of both at once. While many other conditions enter into the degree of the deviation of the complement besides the clinical symptoms (and we should remember that severe, apparently essential anemia may be the dominant clinical note in an otherwise quiescent chronic sprue with a nevertheless strong positive serologic reaction), it seems of importance to see how far the degree of the complement deviation accords with the clinical manifestations.

The cases noted in the following table under the heading "Quiescent" are not to be interpreted in the sense that active symptoms had not been personally verified by me and that the word of the patient had been taken for past symptoms justifying a diagnosis. On the contrary the diagnosis has been made on the conditions at

first found and from the intimate acquaintance of the physician with his patient throughout a long period of time, although, of course, past history has been given due weight in substantiating that diagnosis. "Quiescent" means that at the time of taking the blood the active symptoms and signs, sore tongue, and intestinal disturbance were absent. "Active" means, on the contrary, that these signs and symptoms, one or both, were present. In general therefore it is fair to conclude from an inspection of this table that in proportion to the intensity of the clinical picture so will be the deviation of the complement, with the frequent exceptions inherent in so delicate an appreciation.

DEVIATION OF COMPLEMENT IN SPRUE.

Clinical degree of sprue.	Active.					Quiescent.					Cured.				
	∓	+	++	+++	++++	∓	+	++	+++	++++	∓	+	++	+++	++++
Mild	0	0	0	0	0	5	5	5	2	3	1	1	0	0	0
Moderate	0	1	0	2	3	1	0	3	2	2	0	0	2	0	0
Severe	0	4	1	4	10	0	1	2	0	0	1	1	2	1	2

Finally, in its relation to the question of group reactions it is well to note that in 40 of the 67 cases positive for Monilia psilosis by the Wassermann technic the serum was tested at the same time against an antigen made from other species. The antigens used were as follows:

1. Antigen, Monilia psilosis, Case IV. This was the case from which the organism was first isolated in 1914 and has always been the type upon which I have checked.

2. Antigen, Monilia psilosis, Case CXXXV, Case 89 of the series.

3. Antigen, Monilia species undetermined, an apparently harmless commensal found a number of times in perfectly healthy persons.

4. Antigen, Cryptococcus species undetermined, orange red in color on solid media and a very frequent and harmless inhabitant of the human intestine in Porto Rico.

5. Antigen, combined species of Monilia, in which all Monilia so far isolated by me in this Island were mixed.

Of 24 reactions of Wassermann type performed with antigens 3 and 4, those with the antigen of Monilia psilosis being positive, 21 were negative. The other three all gave a 100 per cent. positive for Monilia psilosis and a + only for one or the other of the antigens of 3 and 4. Of 16 Wassermann reactions performed with antigen 3 alone, 15 were negative and one with a 100 per cent. positive for Monilia psilosis gave a +.

The Clinical Histories. These have been briefed from a question form identical for each case.

THE AGE.

Years.	Cases.
1 to 9	1
10 to 15	1
16 to 30	26
31 to 50	33
Over 50	7

It might be deduced from this table that sprue is *par excellence* a disease of the prime of life, but in reality it is not so restricted. On

account of the difficulties attendant upon obtaining sufficient blood for the serological tests in the very young, cases under fifteen years had to be usually omitted. Specific intestinal moniliasis is fully as common among children as adults. A goodly proportion of acute and chronic enterocolitis of children in cities, in a country where practically all milk is boiled, are due to Monilia psilosis.

Sex. Males, 26 cases; females, 42 cases. Whether this proportion will hold good for a larger number is problematical. In Porto Rico, as in most countries, women eat more sweets than men, and their tendency to live their lives within four walls undoubtedly lessens their resistance to the effects of a chronic infectious disease like sprue.

Color. Whites, 55; mulattos, 13. Sprue seems to be a rare disease among negros.

COUNTRY.

Porto Rico	48 cases
United States	10 "
Spain	4 "
Syria	3 "
English Antilles	1 case
Santo Domingo	1 "
Venezuela	1 "

All foreigners give a clear history of having been infected a short while after reaching Porto Rico, with the exception of Dominicans. In Santo Domingo the disease is believed to be prevalent in towns, as seen from many cases outside of this series. That sprue is more prevalent among foreigners is clear, as the proportion to Porto Rican residents is not above 1 to 50 of the population in San Juan, and the type of the disease in the former is apt to be more severe.

ECONOMIC POSITION.

Poor	8 cases
In modest circumstances but able to secure an ample food supply	27 "
Well-to-do	28 "
Wealthy	5 "

Sprue is an urban disease and is much more prevalent among those who are able to live well. Therein it differs from pellagra. Its comparative rarity in the country districts among the poor laborers is seen in the result of a careful survey of 10,140 country people in Utuado in 1914, among whom only 11 cases of complete sprue and 19 doubtful cases were seen. The majority of these 30 cases lived in the town of Utuado and not in the country.

OCCUPATION.

Motorist	1	Mayor Domo Sugar Central	1
Housewife	31	Petty Officer, Federal Service	1
Fruit grower	1	Laborer	2
Sugar planter	2	School girl	2
Merchant	2	Society girl	1
Pedlar	1	Chief Engineer, Sugar Central	1
Servant	2	Policeman	1
School teacher	5	Stateman	1
Convict	1	Supervisor schools	1
Navy Officer	1	Collector rents	1
Sister of Charity	2	Artisan	1
Sergeant, U. S. Army	1	Justice of Court	1
Shop girl	2	No occupation	2

DURATION OF THE DISEASE WHEN EXAMINED.

1 month or less	4 cases
1 to 3 months	0 "
4 to 6 months	6 "
7 months to a year	6 "
2 years	8 "
3 years	4 "
4 years	12 "
6 to 10 years	8 "
11 to 15 years	7 "
Over 15 years	7 "
Not stated	6 "

Prevalence of Sprue in Other Members of the Same Family. In 36 cases other members of the family were at the same time suffering from or had presumably had sprue. Sprue is undoubtedly a communicable disease, much as is tuberculosis, in this sense.

The Onset of Sprue. The investigation of these 68 cases has revealed what few if any works on sprue mention, namely, that the onset is often acute and can be dated from a severe "indigestion," "descomposicion," or other acute and often violently inflammatory condition of some part of the upper intestinal tube. This is borne out by the following notes on the mode of onset in these cases:

As food poisoning	1 case
Acute, as gastro-enteritis	22 cases
Acute gastritis	1 case
Acute stomatitis	4 cases
Acute duodenitis	1 case
Total acute cases	29 cases
Urticaria, nausea, bad taste in mouth	1 case
Lassitude, fever, sore throat	1 "
Anemia	1 "
Gradually, with gaseous indigestion	28 cases
No symptoms	1 case
Total beginning gradually	32 cases
Failed to remember how disease began	7 "

Type of the Disease. It is very evident that what we have been describing as "sprue" from the days of Hillary to date is really the terminal phase of sprue. In the *Am. Jour. Trop. Dis. and Preventive Med.*, July, 1915, vol. iii, No. 1, pp. 32–46, "Is Sprue a Moniliasis of the Digestive Tract?," the writer remarks, in connection with the prevalence of "chronic fermentative indigestion" in Porto Rico:

". . . But many (cases) seem to me to be the début of that disease we call 'sprue,' and what I am rapidly coming to believe is merely the terminal phase of a condition commonly disappearing before reaching serious proportions, in this stage of début, as a rule easily controllable from a dietetic stand-point. . . . If we consider that a proportion of the many cases characterized by the 'chronic fermentative indigestion' described are really mild sprue, then we may believe that the disease is usually benign and tends to spontaneous cure."

That this is borne out by my experience here is beyond question.

Therefore, here we have again another point of resemblance to tuberculosis, a disease once only recognized in its ultimate stage, usually that of cachexia, all the preceding stages being covered by a series of glittering generalities, such as "chronic bronchitis," "bronchopneumonia," "grippe," etc., even to "malaria," diagnoses often prompted by whatever superficial condition the "clinical eye" might light on.

But in this series a strict accountability has been had in clinical appreciation: 50 of the 68 cases were complete sprue, incapable of being mistaken even by the dogmatic for any other disease; 18 were cases of incomplete sprue in which either the typical tongue, the typical stools, or the small liver were missing. That these were true sprue there is no reasonable doubt in my own mind, and I hope that there may be none in those who peruse these histories.

Of the 18 cases of incomplete sprue the tongue was always normal in 8; there was no history of diarrhea in 2; and in 12 the liver appeared normal. This organ was small in the other 56 cases. Cachexia was seen in 40 of the 68 cases; a decided sallow color in 10; in 18 no cachexia nor sallowness was observed.

Although the time is too short in the majority to record results of treatment, to date 24 have been apparently cured; 36 are improved, some notably and rapidly so; 6 are still unimproved; 1 was not treated; 1 has just begun treatment.

The type of the disease is expressed in these cases as follows:

Acute	3 cases
" moderate	1 case
" severe	2 cases
Subacute, mild	1 case
" moderate	1 "
" severe	2 cases
Chronic, mild	15 "
" moderate	12 "
" severe	19 "
" intense	8 "
Larval sprue	1 case
Carrier sprue	1 "
Convalescent from sprue	3 cases

CASES NOT SPRUE.

Cancer of the stomach	1 case
Chlorosis	2 cases
Chronic enterocolitis	3 "
Paralysis agitans	1 case
Rheumatic gout	1 "
Hypertrophy of the heart	1 "
Ulcer of leg	1 "
Tuberculosis of lungs	2 cases
Estivo-autumnal fever	2 "
Pellagra	4 "
Stomatitis, lips	1 case
Syphilis	3 cases
" and alcoholism	1 case
Vitiligo	1 "
Neurasthenia	2 cases
Nervous dyspepsia	1 case
Gonorrhea	1 "

Of these cases, 8 stated that cases of sprue existed in their families, the rest denied the existence therein.

In 7 of the 32 the liver was distinctly small. In 13 only species of Monilia other than Monilia psilosis were isolated and yet the serological test with the antigens of Monilia psilosis were absolutely negative, save in cases 25, 46, 50, and 59, two with + reactions and two with ∓.

As to pellagra and the deficiency theory there has been no confusion with that disease in this series, although the danger of such confusion is not to be overlooked when the skin lesions of pellagra are absent. Before the popular knowledge of the existence of pellagra in the United States, even among American physicians, Dr. W. W. King, Dr. Pedro Gutierrez and myself were conversant with its manifestations and reported, as the Porto Rico Anemia Commission, a case in our series for Uncinariasis in 1904 (Anemia in Porto Rico, Government Printing Office, San Juan, P. R., December, 1904). Since that time we have had ample opportunity to observe that while present here it is by no means a common disease. Practically all of the people of Porto Rico eat beans in plenty, no matter how poor or how rich, and this is one of the first lessons the tourist learns, a fact to which our attention was especially directed by Dr. Michel, who has worked intensely on pellagra in the South of the United States and who is as decided as are we that pellagra is not a common disease in Porto Rico. Meat was a common article of diet among the cases which form the basis of this paper, and I have purposely assured myself that the full 95 per cent. could not be taxed with the charge that vitamines were lacking in their diet. It would have to be some mysterious sort of vitamine if such lack existed. Of course, the writer has not lost sight of the justifiable suspicion in connection with food unbalance in that lack of unidentified vitamines or excess of certain classes of foods may tremendously affect the manifestations of chronic infectious processes initiated and sustained by organisms of comparatively little potency. The epochal work on vitamine deficiency seems to be as yet in its infancy.

The skin manifestations of pellagra were missing and the mental symptoms were not comparable to those of pellagra, save in one case. It is not therefore to be ignored that we of this institute who live our medical life here quite as intensely as our confrères in the North, who are unconversant with our local problems, are willing to be deceived by so gross an error in observation. Quite on the contrary the cases of pellagra are clearly diagnosed in this series, and they are all negative for Monilia psilosis, and all but one (a faint positive) are negative also when submitted to the Wassermann test for sprue. That cases of "pellagra sine pellagra" exist—cases by the way which are violently contested by authorities on pellagra—can only be resolved, I believe, by accepting the etiology of sprue as herein recorded and thus clearing up a question until now unanswered.

A STUDY OF TOXINS AND THE SEROLOGICAL REACTIONS IN SPRUE.

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Ashford having shown the relationship of the Monilia psilosis to clinical sprue the necessity of studies of the biological activities of the Monilia psilosis as differentiated from other Monilia led to the use of various serological tests.

Very little being known about the disease-producing substances of the Monilia, experiments were made to determine the toxic substances of the Monilia and what substance could be used as a suitable constant antigen in the tests.

The Toxins. Cultures of virulent Monilia psilosis which had been isolated from fatal cases of sprue, and which, when inoculated (10 c.c.) into a guinea-pig killed it in forty-eight hours, were used. The culture was made on glucose-bouillon incubated forty-eight hours, then shaken in a machine for four hours, and filtered through a Berkefeld filter. From 2 to 10 c.c. of the filtrate were injected into several guinea-pigs. The animals at no time showed toxic symptoms or signs of infection. The same experiments were repeated with emulsions of cultures grown on solid media, and no symptoms of toxemia or infection appeared, which showed that no soluble toxin was present and that the toxin elaborated by Monilia psilosis is not extracellular. As a control, 5 c.c. of the unfiltered culture was injected into a guinea-pig, killing the animal in fifty-six hours. The Monilia was recovered from the heart, spleen, and liver. These experiments led to the study of the Monilia proteins and endotoxins.

Cultures of the Monilia being very difficult to kill, owing to the thermal death-point, which normally is 75° for ten minutes, and as that temperature is injurious to the antigenic enzymes, autolyzation was used as a means to lower the thermal death-point. Cultures of Monilia psilosis were autolyzed by suspending in distilled water, using one six-day culture to 10 c.c. of water. The emulsion was incubated for four days, after which 0.5 per cent. phenol was added and heated to 58° C. for forty-five minutes. Cultures made of the emulsion showed it to be sterile. The emulsion was filtered through a Berkefeld filter and 10 c.c. injected intraperitoneally into a guinea-pig. Slight toxic symptoms were observed from which the animal recovered within twenty-four hours. Five c.c. of the unfiltered emulsion injected intraperitoneally caused an animal to become severely sick with severe diarrhea and toxic symptoms, the animal losing 20 grams within two days. On the third day the symptoms subsided and the animal recovered.

An emulsion of Monilia psilosis was prepared, autolyzed, and killed, one four days slant culture growth being used for each 10 c.c. of 0.5 per cent. phenol solution. Animal and cultural tests were made to test its toxity and sterility. Fifteen persons, who gave no clinical symptoms of sprue and who in no way had been exposed to the disease, were injected. Each person was injected subcutaneously with 0.15 c.c. of the emulsion. A slight local reaction was noticed at the site of injection, which lasted about eighteen hours and then gradually disappeared, leaving a small indurated area. In one case there was a slight rise in temperature which dropped after forty-eight hours.

Several persons who had typical sprue were each injected with 0.1 c.c. of the emulsion. A pronounced reaction resulted and there was an aggravation of all the sprue symptoms. The reaction lasted for three or four days and slowly subsided. The local reaction persisted for five days. This showed that the Monilia proteins and endotoxins were to be considered as the active toxic substances in sprue, and would be of greatest antigenic value, and that these substances have the power to stimulate the production of antibodies in man.

Agglutination Reaction. To determine the specificity of the Monilia an agglutination test was used.

Two rows of tubes were set up, each containing 0.1 c.c. of normal salt solution. The serum of a clinically and culturally positive case of sprue was added in dilutions of 1 to 10, 1 to 5, and 1 to 2. To this was added 0.2 c.c. of a strong Monilia psilosis emulsion. In the other row normal serum was used as a control. The tubes were incubated eighteen hours and the results observed. In the tube which contained 1 to 2 dilution of positive serum a flaky precipitate was found upon slight agitation. The tubes containing the normal serum, upon agitation, remained uniform. Using this test as a basis a number of tests were made in which an emulsion of a Cryptococcus and normal serum were used for controls.

It was found that the agglutination test using the Monilia emulsion and known sprue serum was positive in only the cases which had severe sprue, with the serum of mild or latent cases the reaction was negative and no perceptible agglutination resulted.

Precipitin tests using Monilia filtrates were tried and did not yield any satisfactory results.

Complement-fixation Test. The complement-fixation test in sprue requires careful interpretation. In order to establish a positive standard, careful preliminary tests were made to determine the specificity of this test to the clinical cases. All of the tests made were checked up clinically and mycologically by Ashford.

Preparation of Antigens. Cultures of Monilia were made on Sabouraud's glucose media, incubated four weeks. The growth was washed off with distilled water, using one culture to 10 c.c.

The emulsion was shaken in a machine for two hours and incubated for four days to allow autolyzation. Half of 1 per cent. phenol was added as a preservative and the emulsion heated to 58° for one hour. Cultures were made as to its sterility. It was then titrated for its hemolytic and anticomplementary action. In the tests 1 c.c. was used as a standard. This emulsion has been used six months and the standard has not changed, which makes it a very stable antigen. Old cultures make the best antigens. Antigens made of young cultures lose their stability. Antigens made from the liver and heart of animals that died of acute sprue were of no value. Liver extracts from a patient dying of sprue gave unsatisfactory results.

Alcoholic Antigens. Emulsions of Monilia made in distilled water and incubated, after which the emulsion was heated to 58° for one hour and shaken in the machine for four hours. The emulsion was centrifuged and the supernating liquid poured off. To 1 c.c. of the sediment 15 c.c. of alcohol were added and incubated for two days. In the tests 1 c.c. of a 5 per cent. solution was used. The antigen showed positive in many cases, but was not constant in the delicate tests. The most preferable antigen is the watery emulsion, which is the most constant. The anticomplementary action of this emulsion is about 0.25 c.c. In the actual tests 0.07 to 1 c.c. was used.

Serum. Serum used was decomplementized by heating for an hour at 56° C., 2 c.c. of serum used. It is advisable to heat all serum to destroy the thermolabile anticomplementary enzymes. If natural only 1 c.c. was used. It is of interest to note that in Porto Rico the complement content of human blood was extremely high as compared to the United States, and heating at the 56° for thirty-minutes did not destroy all the complement. This was overcome by heating the blood at 56° for an hour and allowing it to stand for at least twelve hours before using.

Complement. In these tests 0.3 c.c. of a 10 per cent. solution of guinea-pig serum was used.

Amboceptor. Antisheep amboceptor $\frac{1}{1000}$ solution of serum titrated so that 1 unit=2 c.c. In the tests $1\frac{1}{2}$ units or 0.3 c.c. were used.

Erythrocytes. 1 c.c. of a 5 per cent. solution of sheep corpuscles were used.

Technic. The technic employed in these tests were the Wassermann, Noguchi, and a modified Wassermann in which concentrated serums were used.

In the Wassermann test two series of tubes were set up. One series containing 0.1 c.c. of normal serum. In the other 0.2 c.c. of inactivated serum was used; 0.7 c.c. of Monilia psilosis antigen was added to each series. A control series of five tubes each was set

up for each test, and the following antigens used; 0.1 c.c. of antigen prepared from a non-virulent Monilia isolated from feces, 0.1 c.c. of a white Monilia antigen, 0.1 c.c. of a red Cryptococcus antigen which was isolated from feces, 0.1 c.c. of a combined antigen prepared from mixture of all the antigens used. Another series of controls using syphilitic antigen was used. To all these tubes 0.3 c.c. of a 10 per cent. guinea-pig serum was added and 1 c.c. of salt solution. The tubes were then heated in a water-bath for half an hour, after which 0.3 c.c. of $\frac{1}{1000}$ antisheep amboceptor and 1 c.c. of 5 per cent. sheep erythrocytes was added. The tubes were again incubated for thirty minutes and the results taken.

In the Noguchi test similar technic was employed, using the same number of controls.

In the modified Wassermann test 1 drop of serum, 2 drops of antigen, 1 drop of undiluted complement and 10 drops of salt solution was placed in each tube. The tubes were then incubated for twenty minutes at 37° C., after which 2 drops of $\frac{1}{1000}$ sheep amboceptor and 0.2 c.c. of 10 per cent. sheep corpuscles were added. The tubes were again incubated for half an hour and the results taken. The Noguchi method proved to be the most delicate, and when this test was negative the cases were also found to be negative mycologically and clinically. In all cases which gave a positive result by the Wassermann reaction the Monilia psilosis was isolated from the feces and the case had clinical symptoms, with the exception of a few described in Ashford's article. The results of all these tests depend upon having proper antigens, and it is noted that antigens prepared from young cultures will not give a pronounced reaction.

SPECIFICITY OF THE TEST. Out of over 400 tests made, including various diseases, all cases which were diagnosed clinical sprue and from which the Monilia psilosis was isolated from the tongue and feces, the complement-fixation test was positive.

The other Monilia antigens used have faintly positive results only in severe cases of sprue. In these tests the results with other Monilia antigen was about 15 per cent. positive, while the reaction with the psilosis antigen was 100 per cent. positive. It is of interest to note that this reaction varies with the condition of the patient. In cases of chronic or latent sprue, and in cases which had recovered, the reaction tends to become negative.

Guinea-pigs which had been injected twice in ten days with 5 c.c. of a non-virulent Monilia psilosis culture gave positive tests, and as the animal recovered the reaction became negative.

Cases which had clinical syphilis and sprue, the fixation test for both these diseases was positive.

Pellagra having been demonstrated by Goldberger as a diet deficiency disease, the same view has been taken regarding sprue. In these series several cases of pellagra were included. All these

cases were severe and had typical symptoms of that disease, and in no case was the Monilia psilosis isolated. The complement-fixation test in all these cases was negative, with the exception of one faintly positive.

Guinea-pig serum of an animal which had been inoculated with a killed culture of Monilia psilosis gave a strong positive reaction.

It is of interest to note that the serum from animals which had been inoculated with live cultures or killed cultures of Monilia psilosis gave the same results as the serum of patients that have sprue, and from which the Monilia psilosis had been isolated from tongue and feces. In view of these results and with Ashford's clinical and mycological work it is strongly evident that the Monilia psilosis of Ashford is the etiological factor in sprue. At the present time tests are being made daily in this laboratory, with the same constant results as described in this article.

THE DISINFECTION OF DRINKING WATER.

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(From the Herter Laboratory, New York.)

The sterilization of contaminated drinking water is a problem of special importance in war time. The use of bleaching powder, or similar hypochlorite or chlorin preparation, has been used with the greatest success for the sterilization of relatively large volumes of water. The use of water carts containing water treated with a carefully regulated quantity of bleaching powder has given every satisfaction when the method could be satisfactorily carried out, as, for example, when troops are practically stationary. The problem of sterilizing small individual quantities of water, such as are needed by cavalry or rapidly moving troops, is a much more difficult problem which, up to the present, has not been perfectly solved. The use of hypochlorites for such purposes is difficult, owing to the instability of small tablets containing the minute quantity of active disinfectant. In their place, acid sulphates of the alkali metals have been extensively used in tablet form, but the superior potency of many chlorin compounds would indicate that a stable potable chlorin disinfectant suitable for the sterilization of small quantities of water was desirable. With this end in view we have made a number of experiments with various types of substances, one of which we believe to be worth practical application.

TABLE I.—EXPERIMENTS WITH P-SULPHONDICHLORAMINOBENZOIC ACID IN TABLET FORM.

No.	Water treated.	Concentration of disinfectant.	Time of action, min.	Surviving organisms, per c.c.	Tablet dissolved, min.
1	Croton water + B. coli	..	..	63,800	
		1 to 200,000	30	0	4
2	Croton water + B. coli	..	..	38,629	
		1 to 200,000	30	0	9
3	Croton water + B. coli	..	..	112,525	
		1 to 200,000	15	0	9
4	Croton water + B. coli	..	..	112,525	
		1 to 250,000	15	0	9
5	Croton water + B. coli	..	..	112,525	
		1 to 400,000	15	0	10
6	Croton water + B. coli	..	..	178,528	
		1 to 500,000	15	987	10
		1 to 500,000	30	0	10
7	Croton water + B. coli	..	..	125,420	
		1 to 500,000	15	406	12
		1 to 500,000	30	0	12
8	Croton water + 5 per cent. sewage + B. coli	..	..	1,119,000	
		1 to 175,000	15	6,000	9
			30	0	9
			60	0	9
9	Croton water + 5 per cent. sewage + B. coli	..	..	1,158,500	
		1 to 330,000	15	120,064	
		1 to 330,000	30	9,146	7
		1 to 330,000	60	0	7
10	Croton water + 5 per cent. sewage + B. coli	..	..	1,120,000	
		1 to 500,000	15	284,800	5
		1 to 500,000	30	49,318	5
		1 to 500,000	60	70	5
11	Deep yellow polluted river water, B. coli	0	..	33,152	13
		1 to 250,000	20	10,940	
		1 to 250,000	40	852	
		1 to 250,000	60	0	
12	Croton water, B. typhosus	0	..	155,400	
		1 to 225,000	20	0	17
13	Hard water + B. typhosus	0	..	85,400	
		1 to 333,333	20	0	14
14	Croton water, 5 per cent. sewage + B. typhosus	0	..	66,017	
		1 to 333,333	20	242	14
		1 to 333,333	40	0	
15	Croton water, 5 per cent. sewage + B. typhosus	0	..	240,000	
		1 to 225,000	20	13	14
		1 to 225,000	40	0	
16	Croton water, B. paratyphosus A	0	..	112,000	
		1 to 225,000	20	0	17
17	Croton water, 5 per cent. sewage, B. paratyphosus A	0	..	138,000	
		1 to 225,000	20	0	13
18	Croton water, 5 per cent. sewage, B. paratyphosus A	0	..	29,400	
		1 to 333,333	20	15	12
		1 to 333,333	40	0	
19	Croton water, B. paratyphosus B	0	..	322,500	
		1 to 225,000	20	10	17
		1 to 225,000	40	0	
20	Croton water, 5 per cent. sewage, B. paratyphosus B	0	..	309,120	
		1 to 225,000	20	305	13
		1 to 225,000	40	0	

TABLE I.—EXPERIMENTS WITH P–SULPHONDICHLORAMINOBENZOIC ACID IN TABLET FORM.—*Continued.*

No.	Water treated.	Concentration of disinfectant.	Time of action, min.	Surviving organisms, per c.c.	Tablet dissolved, min.
21	Croton water, 5 per cent. sewage, B. paratyphosus B	0	..	139,776	
		1 to 333,333	20	290	12
		1 to 333,333	40	0	
22	Croton water + V. choleræ	0	..	13,706	
		1 to 400,000	20	0	12½
23	Croton water, 5 per cent. sewage, V. choleræ	0	..	11,170	13
		1 to 333,333	20	0	
24	Croton water, B. dysenteriæ (Flexner)	0	..	66,998	
		1 to 450,000	15	25	13
		1 to 450,000	30	0	
25	Croton water, B. dysenteriæ (Flexner)	0	..	98,990	
		1 to 333,333	20	17,363	7
		1 to 333,333	40	58	
26	Croton water, 5 per cent. sewage, B. dysenteriæ (Flexner)	0	..	164,864	
		1 to 333,333	20	38	13
		1 to 333,333	40	0	
27	Croton water, B. dysenteriæ (Shiga)	0	..	33,852	
		1 to 450,000	15	12,227	6
		1 to 450,000	30	1,080	
28	Croton water, B. dysenteriæ (Shiga)	0	..	31,200	
		1 to 333,333	20	10,934	11
		1 to 333,333	40	0	
29	Croton water, 5 per cent. sewage, B. dysenteriæ (Shiga)	0	..	2,108	
		1 to 333,333	20	0	13

Our first experiments were made with chloramin-T,[1] but it was found that when this substance was added to heavily contaminated waters it required a relatively high concentration to sterilize the water promptly, particularly in the case of hard alkalin waters. For example, 1 part of chloramin-T to 25,000 parts of water may be necessary, and such an amount is decidedly unpalatable. Subsequently, it was found that much lower concentrations of chloramin-T were effective if the contaminated water was slightly acidified with any acid, *e. g.*, citric, tartaric, acetic, etc. Under these conditions, 1 to 250,000 or less of chloramin-T was effective (see Table III), and the resulting water was not unpleasant to the taste. But chloramin-T could not be made up in a tablet with the addition of an acid without decomposition, and the two-tablet system was regarded as impracticable.

Subsequently, we experimented with preformed toluenesulphondichloramins, since a substance of this type is formed on adding acid to chloramin-T. The early results were most encouraging (see Table II), and it was not until we had the product put up in tablet form that we found it to be unsuitable. The difficulties were twofold: (1) When the small necessary quantity of dichloramin

[1] The abbreviated name for sodium toluene-p-sulphochloramide, Cf. British Med. Jour., January 29, 1916. Proc. Roy. Soc., B., 1916, lxxxix, 232.

(0.002 gm. for 0.5 liter of water) was mixed with what were assumed to be inert salts, *e. g.*, sodium chloride, for making into small tablets the very slow normal rate of decomposition of the dichloramin was greatly accelerated. (2) The dichloramin, after dispensing in tablet form, became too insoluble to effect prompt sterilization. The substance had therefore to be abandoned and we turned our attention to a search for similarly active compounds which would show greater stability and solubility.

TABLE II.—EXPERIMENTS WITH O– AND P–TOLUENESULPHON-DICHLORAMIN IN POWDER AND TABLET FORM.

No.	Water treated.	Concentration of disinfectant.	Time of action, min.	Surviving organisms per c.c.	Form of disinfectant.
1	Croton water + B. coli	..	..	11,520	
		1 to 250,000	7	680	*o*-, powder.
		1 to 250,000	15	0	
2	Croton water + B. coli	..	..	40,980	
		1 to 250,000	7	20	*o*, powder.
		1 to 250,000	15	4	*o*, powder.
		1 to 250,000	30	0	*o*, powder.
3	Hard water + feces, suspension	..	..	22,080	
		1 to 250,000	7	200	*o*, powder.
		1 to 250,000	15	0	*o*, powder.
4	Hard water + 10 per cent. city sewage	..	..	64,000	
		1 to 250,000	7	448	
			15	210	
			30	74	
			60	2	
5	Croton water + 2.5 per cent. city sewage	..	..	6,420	
		1 to 250,000	7	0	*o*, powder.
6	Croton water + 5 per cent. sewage	..	..	18,300	*p*, powder.
		1 to 250,000	7	1,644	
		1 to 250,000	15	455	
		1 to 250,000	30	0	
7	Croton water + 5 per cent. sewage	..	..	18,300	*p*, powder.
		1 to 500,000	7	11,928	
			15	2,600	
			30	930	
			60	0	
8	Croton water + 5 per cent. sewage	..	..	18,300	
		1 to 1,000,000	7	19,405	*p*, powder.
		1 to 1,000,000	15	18,920	
		1 to 1,000,000	30	7,024	
		1 to 1,000,000	60	630	
9	Hard water + B. coli	..	..	161,000	
		1 to 200,000	10	166,400	*p*, tablet.
		1 to 200,000	40	105,288	
		1 to 200,000	60	56,160	

The substance which is the most suitable that we have yet found is p-sulphondichloraminobenzoic acid, $Cl_2N.O_2S.C_6H_4.COOH$. It is easily prepared from cheap, readily available materials, and appears to be effective and reasonably stable. The presence of the COOH group confers a slightly greater degree of solubility

in water, which is increased by dispensing it with alkaline salts such as sodium carbonate or bicarbonate, borax or sodium phosphate. Formulæ for the tablets are appended, together with details of the preparation of the substance and an estimate of its cost.

TABLE III.—EXPERIMENTS WITH CHLORAMIN-T, WITH AND WITHOUT ADDITION OF TARTARIC OR CITRIC ACID.

No.	Water treated.	Concentration of disinfectant.	Acid added, gm. per liter.	Time of action, min.	Surviving organisms per c.c.
1	Hard water + B. coli	..	..	..	2,508,800
		1 to 25,000	None	10	35,200
		1 to 25,000	None	30	14,880
2	Hard water + B. coli	..	..	..	1,120,000
		1 to 300,000	0.4	10	180
		1 to 300,000	0.4	30	0
3	Hard water + B. coli + 0.1 per cent. feces	..	0.8	..	3,232,000
		1 to 200,000	0.8	10	0
4	Hard water + B. coli	..	0.2	..	520,000
		1 to 250,000	0.2	10	27,200
		1 to 250,000	0.2	30	7,200
		1 to 250,000	0.8	10	130
		1 to 250,000	0.8	30	50
5	Hard water + V. choleræ	..	..	..	744,000
		1 to 250,000	0.8	10	0
		1 to 500,000	0.8	10	0
6	Hard water + B. typhosus	..	..	..	345,000
		1 to 500,000	0.8	10	1,760
		1 to 500,000	0.8	30	0

Since the systematic name of the disinfectant is inconveniently long for ordinary use we propose to apply the name halazone to the tablets containing it. This abbreviated name gives some indication of the character of the compound.

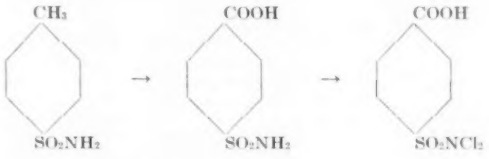
In Table I are given some of our bacteriological results. The technic employed was that in general use, and requires no special description. Five to ten standard drops of the treated water were generally used for plating on agar and counting the surviving organisms. Suitable controls were invariably carried out.

From the results in Table I it appears that a concentration of 1 to 300,000 is sufficient to sterilize an ordinarily heavily contaminated water in about thirty minutes. Such a concentration could be relied upon to remove coli, typhoid, or cholera organisms. Special experiments showed that the substance in tablet form was efficacious when acting on water contained in aluminum bottles, although a very trifling action on the metal may be observed if tablets are allowed to remain undisturbed in long contact with the metal. We believe such action to be of no practical moment. The concentration of the disinfectant given above is just perceptible to the taste, especially in warm waters containing little organic matter; but the water is perfectly palatable.

The point of advantage of the present disinfectant over most hypochlorite preparations is the fact that the active chlorin is less rapidly used up, so that the process of disinfection continues for a longer period.

Preparation of p-Sulphondichloraminobenzoic Acid. The starting-point in the preparation of this substance is p-toluenesulphonamide, a product which is readily obtained by the action of ammonia on p-toluenesulphonic chloride. The latter substance is a very cheap waste product in the manufacture of saccharin, and is available in relatively large quantities. It is now used for the manufacture of chloramin-T.

Toluenesulphonamide is oxidized to p-sulphonamidobenzoic acid, and the latter substance on treatment with chlorin under suitable conditions gives the desired dichloraminoacid. The reaction may be expressed as follows:



The experimental details are as follows:

Preparation of p-Sulphonamidobenzoic Acid. Add 250 grams commercial sodium dichromate to a mixture of 200 c.c. concentrated sulphuric acid and 600 c.c. water contained in a 2-liter round flask. Then add 100 grams crude toluene-p-sulphonamide and heat on a sand-bath with reflux condenser for one hour, using a small flame at first, as the reaction is vigorous. On cooling, wash the separated crystals well with cold water and then dissolve them in hot dilute sodium hydroxide in slight excess. Filter hot and add excess of hydrochloric acid, and when cold filter off the precipitated acid and wash well with water and dry. The yield is about 80 per cent. of theory. (Cf. Remsen: *Ann.*, 1875, clxxviii, 298.)

Preparation of p-Sulphondichloraminobenzoic Acid. Twenty grams of p-sulphonamidobenzoic acid are dissolved in 200 c.c. approximately normal sodium hydroxide (2 molecules), warming if necessary. About 200 grams of crushed ice is then added and the mixture saturated with a rapid current of chlorin. The reaction is most conveniently carried out in a fairly wide-mouthed flask, which may be shaken while the gas is being introduced. If the temperature should rise materially more ice can be added. A white, rather chalky precipitate of the dichloraminoacid is at once precipitated. The acid is filtered off, using suction, well washed with cold water, and dried *in vacuo* on a porous plate. The dry substance is practically pure, and may be powdered and preserved

apparently indefinitely. Prepared by this method the yield of the dichloraminoacid is practically the theoretical amount (26.86 grams).

The substance is sparingly soluble in water and in chloroform and insoluble in petroleum. It readily dissolves in glacial acetic acid, crystallizing in stout prisms, which melt at 213° C. The substance explodes feebly when rapidly heated on platinum foil, but, compared with most members of the group, is remarkably stable.

The purity of the compound may be checked by titration as follows: 0.1 gm. is weighed out, dissolved in glacial acetic acid and potassium iodide added. The liberated iodin is titrated with decinormal sodium thiosulphate, of which 14.8 to 14.9 c.c. will be required.

The dichloraminoacid dissolves, apparently without change, in excess of cold sodium hydrate solution, and may be reprecipitated on addition of acids. With smaller quantities of sodium hydroxide or with feebly alkaline salts, such as phosphates or borates, hydrolysis occurs with liberation of disagreeably smelling compounds of nitrogen and chlorin.

Preparation of Tablets. We have observed no very marked differences in the behavior of the sulphondichloraminobenzoic acid when made into a tablet with salt and either sodium carbonate or bicarbonate, dry or crystallized borax, or sodium phosphate, although the crystallized or hygroscopic salts are undesirable if the tablets are exposed to high temperatures. The sodium carbonate or dry borax tablets seem as satisfactory as any, and a convenient formula for tablets weighing 100 to 105 mg. is to use sulphondichloraminobenzoic acid 4 per cent. dry, sodium carbonate 4 per cent. (or dried borax 10 per cent), sodium chloride (pure) 92 per cent. The acid should be ground up with the dry salt and the sodium bicarbonate added subsequently. The mixture may be passed through a 40-mesh sieve. No lubricant or other addition is necessary, and should be avoided. The strength of the tablets should be tested by dissolving in acetic acid and potassium iodide solution and titrating with sodium thiosulphate as already described (1 c.c. $\frac{N}{10}$ thiosulphate = 0.00675 gm. of the dichloramino acid). They must not be allowed to dissolve in water and subsequently titrated, as then decomposition occurs. The tablets should be stored in small amber glass bottles.

Tablets so prepared, of the weight mentioned, contain about 4 mg. of the disinfectant, and are suitable for the sterilization of 1 liter or 1 quart of reasonably heavily contaminated water. In the case of extreme contamination a second tablet may be necessary.

Stability of Tablets. The practical success of the disinfectant we propose will depend very largely on the stability of the tablet. At present, sufficient time has not elapsed for entirely convincing

experiments, but it appears, as judged by a very few months' observation, that the stability of the tablets is great enough so as not to destroy their practical value. They are certainly more stable than other similar compounds with which we are acquainted. When kept in amber bottles under ordinary conditions no decomposition was noted in two months. When exposed to bright sunlight, in clear glass tubes, decomposition was more marked, and the same was true of the crystalized borax tablet at a temperature of 38° C. The dried borax and sodium carbonate preparations were stable under these conditions, the bicarbonate ones less so. On the whole the dry borax or dry sodium carbonate tablets appear preferable.

Cost. It is rather difficult to give precise estimates of the cost of the finished product, but it could doubtless be supplied at such a figure that 100 gallons of water could be sterilized at a cost of two cents; the cost of manufacture should not greatly exceed that of chloramin-T, which is manufactured and sold retail at $3 per pound in England and about $4 per pound in the United States. At this figure the cost of the disinfectant for 1,000,000 pints of water would be in the neighborhood of $12 to $16. No allowance is made in this calculation for the cost of tablet manufacture, but this would be a small item.

CONCERNING THE INDICATIONS FOR AND DANGERS OF TONSILLECTOMY.

By George B. Wood, M.D.,
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The operation of tonsillectomy has become a well-recognized and perfectly justifiable procedure; indeed, it is now one of the most, if not the most, frequently done surgical operation. Not only does it constitute the bulk of the operative work of the nose and throat specialist, but large numbers of tonsils are removed by surgeons and general practitioners. It is true that in a great many cases the operation is easy, presents no special difficulty, and is not followed by any serious disturbances. Yet, on the other hand, it is not free from danger by any means, and even death, as a direct result of the operation, is entirely possible, and in fact many such deaths have occurred. We must admit, however, that the percentage of fatal results is exceedingly small when we consider the enormous number of these operations that are done throughout the country. Other more or less serious complications are more frequent, so that while the benefit that frequently accrues from the removal of an infecting tonsil distinctly outweighs the risk of the operation, it is essential to have a clear understanding of the indications and dangers before submitting any patient to this risk.

Theoretically, the indications for the removal of the faucial tonsils may be divided into two classes: (1) those in which the tonsils are responsible for local disturbances, and (2) those in which the tonsils act as a gateway of entrance for a systemic infection. Usually, however, a tonsil which produces local disturbances also affects the constitution more or less gravely, although the converse of this does not hold as many small unimportant looking tonsils, locally benign, are the seat of hidden but serious focal lesions.

It is seldom that the indications for the removal of the tonsils are so absolute as to demand immediate intervention, yet it is conceivable that an acute inflammation of unusually large tonsils may bring about serious interference with respiration. It is advisable, under these circumstances, to remove one or both of the tonsils rather than to do a tracheotomy.

Patients suffering from repeated attacks of suppurative tonsillitis (the so-called follicular disease), or those who have recently had one or more attacks of peritonsillar abscess, should undoubtedly have their tonsils removed. If any of the tonsillar attacks are followed by infectious processes in other portions of the body, localized or general, surgical interference becomes all the more imperative. Yet we must remember that patients who have recurrent tonsillitis usually but not always have their attacks at fairly frequent intervals for a period of about ten years. Then either because the patient has established some form of immunity against these attacks, or for some peculiar change in the tonsil itself, the attacks become less severe, less frequent, and gradually cease. No matter at what time of life the attacks begin, there seems to be the same cycle of years of repeated attacks, and at the end a cessation of the disease. This biological fact is very important when it comes to the advisability of operative interference.

Tonsillar enlargement is not necessarily an indication for operation unless the extent of hypertrophy is extreme, giving rise to obstructive symptoms. Yet a greatly enlarged tonsil is more frequently the sourse of systemic infection, and, on the whole, is more apt to be repeatedly inflammed than the smaller one. When the enlargement of the tonsils extends upward and outward into the palate the upper surface of the palate may be raised so as to distinctly interfere with Eustachian drainage, a condition which predisposes to otitic disturbances. Also, it must be remembered that embedded tonsils may reach an enormous size and still appear comparatively insignificant under casual inspection.

When patients are to be subjected to etherization for the removal of an enlarged pharyngeal tonsil (adenoids) it is best at the same time to remove the faucial tonsils if there is the slightest indication of trouble originating from them, except when that trouble is insignificant and there is a distinct reason for avoiding any more surgery than necessary or in children under two years of age.

The occurrence of large masses of accumulated debris in the tonsillar crypts often calls for tonsillectomy, but this condition is frequently found in normal healthy individuals with the production of little or no distress except perhaps for a slight local discomfort. Sometimes these cases can be kept under control by appropriate local treatment, but a cure is seldom accomplished without some form of operative interference.

The most difficult type of cases in which to advise patients wisely is those in which there is reason to suspect that the tonsils may be responsible for some cryptogenic toxemia.

First of all we must recognize that the tonsil is not the sole source for the absorption of infectious material, and that unless specific conditions exist as to the etiological importance of the tonsil, these other sources must be sought for and eliminated before judgment is passed. If there is a history of arthritis or other constitutional disturbance following directly upon tonsillar inflammation, and the crypts of the tonsils contain large quantities of cheesy debris, with enlargement of the tonsillar lymph nodes, the responsibility of the tonsils would be practically established. Yet there exist other cases of systemic intoxication in which the infection has come through the tonsils and in which neither by the history nor by direct inspection can any tonsillar abnormality be found. Between these two extreme classes of cases are many others in which by careful study not only of the local appearances of the tonsils but also of the history of the case one may find important connecting data. It must be admitted, however, that the decision to operate often is determined by excluding other sources of infection. Considerable help can often be had by taking cultures from the crypts of the tonsil, but this must be done carefully. A simple technic follows: anesthetize with a 10 per cent. solution of cocain and after a five-minute interval apply tincture of iodin to the surface of the tonsil. The tongue should be held firmly depressed and the patient urged not to gag or to swallow. A small sterile firmly wrapped cotton applicator is passed into the mouth of the crypt through the iodinized surface, an effort being made to obtain material from the bottom of the crypt. As soon as this has been placed back in the tube, and before the patient has swallowed or gagged, a second sterile applicator should touch the surface of the tonsil in the region of the crypt for a control inoculation. Cultures made in this way frequently show pathogenic organisms in pure growth. Sometimes these organisms when tested with the patient's blood will give some biological reaction indicative of their etiological importance to the systemic condition.

When, in spite of the most careful studies, there still exists a doubt as to the role played by the tonsils the decision for or against operating should depend upon the severity of the general condition. In cases of arthritis deformans, of recurrent attacks of acute

rheumatoid arthritis, or some equally severe general infection, if any suspicion, no matter how small, can be placed upon the tonsils the patient should be given the benefit of the doubt and complete enucleation carried out. It is the severity of the general condition that warrants our interference and placing the patient under a certain amount of surgical risk. It is absolutely essential that the specialists work in association with the general practitioner in determining the advisability of the tonsil operation in these cases.

THE DANGERS OF TONSILLECTOMY. It is not probable that the absence of the tonsillar tissues in the throat is ever prejudicial to health. Theoretically, the tonsillar tissue is of importance to the child in its early development, that is, before two or three years of age; but personally I have never seen any harm caused by either the removal of the faucial or pharyngeal tonsils except that which is due directly to the operation.

The choice of an anesthetic is important. In children, general narcosis is always advisable, and ether given by the open method is the safest anesthetic to use. The nitrous oxide-ether sequence is advisable in adults, but it is not safe in children. At the time when the nitrous oxide is stopped and the ether begun not only may there be a temporary suspension of respiration, but sometimes marked weakening of the heart action may develop even to a temporary absence of the wrist pulse. It should never be used in children under ten years of age.

The use of chloroform in tonsillar operations is absolutely unjustifiable even when given by a skilled anesthetist. Sudden death directly attributable to the chloroform itself has occurred too frequently to justify its use simply because of its convenience of administration.

Acidosis due to a general anesthetic follows more often after chloroform than after ether, but I have seen one case following a comparatively short and light ether narcosis in which the child was very ill and narrowly escaped death. The symptoms of severe acidosis do not usually begin until twenty-four hours after the operation, and may occur up to three days. Apparently those occurring at a later period are more severe and very apt to be fatal. Belonging to this group are the cases of delayed chloroform poisoning.

A slight degree of acetonuria is not an uncommon condition following ether anesthesia. It is transient and not accompanied by any severe symptoms. Vomiting, however, is usually prolonged and recovery is somewhat delayed. To guard against this, bicarbonate of soda in large doses should be given for twenty-four hours before the operation. The routine use of bicarbonate of soda has given very gratifying results, reducing the vomiting to a minimum and apparently making the postoperative sore throat less painful.

In selected cases local anesthesia in adults by the infiltration method is almost ideal, except that it is difficult to obtain complete

anesthesia, and in individuals with irritable throats it is often impossible to do a satisfactory operation. Also, if there is a severe hemorrhage the bleeding is much more difficult to control and may eventually require general anesthesia.

Possibly the most disagreeable accident of the tonsillar operation is hemorrhage. In the majority of cases of bleeding following tonsillectomy when moderately profuse is venous, and comes from an irregularly disposed group of veins found most frequently just below the tonsil or in the posterior pillar, rarely externally or in the anterior pillar. These veins at times are of considerable size, so that bleeding following their rupture may be quite profuse. Fortunately, this form of bleeding is easily controlled and stops entirely while slight pressure is being made with the gauze sponge. Generally when the gauze is removed the bleeding recurs only slightly and soon ceases, but sometimes the veins are sufficiently large to require either twisting with a hemostat or ligation. If the bleeding-point can be seen after retracting the anterior pillar a hemostat is generally easily applied. Sometimes a loop of catgut can be slipped over the hemostat, and with the two index fingers deep in the throat the vessel may be tied-off just as is done in ordinary wounds. This, however, may be exceedingly difficult or practically impossible, and then a suture should be passed through the tissues immediately above the point of the hemostat. The introduction of the suture is most easily accomplished with a short, strong curved needle with a round point. This is held in the needle holder with the point toward the handle. The point is inserted posteriorly to the vessel and hooked forward. When the point reappears it can be easily grasped with a hemostat, and when released from the holder the suture is readily drawn through. When, as sometimes happens, the exact bleeding-point cannot be determined, a gauze sponge should be placed in the wound and held in position by suturing the pillars over it. If the removal of the tonsil has left an uncommonly deep and narrow fossa it may not be necessary to insert the suture because the gauze sponge is held sufficiently firmly in position by the tonsillar pillars. A silk thread should be tied to the sponge and the end secured on the cheek with a piece of adhesive plaster, This insertion of a gauze sponge into the tonsil wound is also a great help during the operation. It can be inserted immediately after the removal of one tonsil and exerts enough pressure to practically leave the field bloodless for the removal of the other one.

Usually the blood supply of the tonsil comes through several small arteries, so that the bleeding from this source is unimportant. If the tonsillar blood supply comes through a single branch the artery will, of course, be fairly large and the hemorrhage profuse and persistent. This vessel is usually found on the external wall just back of the anterior pillar, near the upper pole of the tonsil, in which position, after retraction of the anterior pillar, it can be easily seen

and picked up. Occasionally the dorsalis linguæ gives off a considerable branch to the inferior pole of the tonsil, and if the tonsil is of large size the artery may be severed close to its emergence from the tongue. The control of hemorrhage in this case may become very difficult, especially as it is hard to determine the source of the hemorrhage, the force of the spurting artery throwing the blood upward along the tonsillar fossa, so that it appears to come from the upper pole. If the point can be seen and picked up all is well and good, but usually extensive packing and suturing of the pillars will be required, and the packing must be so placed as to exert pressure on the exact spot on the base of the tongue.

In the healthy individual it is doubtful whether death will ever occur from hemorrhage when the bleeding comes from such vessels as above described, though the patient may become badly depleted. On the other hand it is within the realm of possibility for the large vessels of the neck to be wounded during a tonsillar operation. Of course, when this happens there is present some rare anomalous condition, probably the most frequent being a tortuous condition of the internal carotid. Several such cases have been reported, and I have seen one case in which a large vessel thought to be the internal carotid could be seen pulsating at the bottom of the tonsillar wound. The large bloodvessel which is sometimes seen pulsating in the wall of the pharynx behind the posterior pillar is almost always the internal carotid artery and not the ascending pharyngeal. The facial artery occasionally before it loops downward to pass around the jaw forms an upward loop which comes in very close proximity to the inferior pole of the tonsil, and though no cases have been reported in which the hemorrhage was proved to be coming from the facial, it is conceivable that it might possibly be injured. Of course, hemorrhage in these cases is shockingly profuse and severe, and only extreme coolness on the part of the surgeon will avert a fatal issue.

While quite frequently a mild degree of infection of the tonsillar wound follows the operative attack in this region, it is remarkable that comparatively few severe infections occur; cases of fatal septicemia, however, have been reported. Probably about 10 per cent. of the cases operated upon show a moderate degree of elevation of temperature, for two or three days following the operation, accompanied by increased sore throat, general malaise, and other indications of a mild degree of sepsis. The appearance of the wound in these cases seldom differs from those running a normal temperature, except that the surrounding tissues are somewhat more reddened and there is generally some edema of the uvula.

Somewhat recently there has been reported a number of cases of abscess of the lung following tonsillectomy, but with one or two exceptions all of these cases have occurred in adults. The method of infection of the lung in these cases is somewhat obscure, though it

seems probable that some of the crypts of the tonsils having contained large numbers of bacteria have been so squeezed during the operation as to force their contents into the throat. This infectious material mixing with the blood or mucus may be inspired, infecting either the healthy lung or what is more likely, some previously diseased area, such as an old tuberculous lesion, which because of its low vitality more readily yields to the bacterial invasion.

The membrane which is seen after injury to the mucous membrane of the throat is not evidence of an infectious invasion of living tissue, but simply a superficial necrosis of the traumatized tissues with a certain amount of fibrinous exudate and numerous leukocytes. There are two important reasons why severe infections seldom result after a tonsillar operation: (1) the wound being perfectly open and free there is no chance for retention of germ-laden secretions, and (2) the action of the saliva is decidedly bactericidal and the constant swallowing removes and prevents infectious accumulations. When there has been a removal of a very deeply embedded tonsil, necessitating perhaps considerable dissection up into the soft palate, we occasionally see a retention of infectious matter due to a healing over of the edges of the wound. This condition somewhat resembles quinsy, but can be easily relieved by separating the edges of the pillars.

One of the more serious complications following as a direct result of postoperative infection is involvement of the ear through the Eustachian tubes. When, however, we consider the mass of infectious material which for days bathes the openings of the Eustachain tubes after an adenectomy the percentage of this complication is surprisingly small. However, middle-ear suppuration directly blamable to the operation on the throat does sometimes occur and may lead to mastoid involvement. A temporary congestion of the drum with a considerable amount of earache is more frequent, but usually clears up within a few days without leaving any serious results.

The chief factor in the production of sepsis of the throat following tonsil operations is excessive trauma, and next to this pyorrhea or other septic conditions of the teeth and gums. Of course, if one operates during an attack of acute infection of the upper respiratory tract he runs a distinct risk of infecting the wound; but unless there is some urgent reason one does not operate under such conditions. In one case in which a tonsillotomy was done during an attack of severe suppurative tonsillitis, because the tissues were so swollen that the patient had distinct dyspnea, the wound did just as well as though it had followed a tonsillectomy done during ordinary conditions.

Deformity of the tonsillar pillars and the soft palate not infrequently follow the tonsil operation, and is usually dependent upon faulty technic on the part of the operator. However, in spite of the most careful surgery there will sometimes be a moderate degree of

cicatricial contraction which may temporarily give rise to a slight amount of pulling sensation in the throat and a peculiar tense look of the velum palati. Also, it sometimes happens that after the operation there is apparent ablation of a portion of the posterior pillar, especially in its upper part, where it merges with the soft palate. This I do not believe to be so often the fault of the operator as to the peculiar anatomy of the individual tonsil and its surroundings. Cases of asymmetry of the soft palate even when no operative work has ever been attempted are not so very uncommon.

In spite of many suggestions to the contrary it is very rare for a permanent vocal or other loss of function to occur as the result of a tonsillar operation. Temporary paralysis of the soft palate either due to a stretching of the muscles or to edema and inflammatory infiltration may, of course, give rise to peculiarities of voice for the time being, and may even be so bad as to permit of a certain amount of nasal regurgitation during swallowing; but these are transient conditions.

Accidental removal of a part or the whole of the uvula, while unfortunate, is not as serious as we are sometimes led to believe, unless the wound is sufficiently large to give rise to a considerable amount of cicatricial contraction. There have been some cases reported in which the tonsillar operation has been so unskilfully if not so brutally carried out that the healing of the throat has been followed by adhesions between the soft palate and the posterior pharyngeal wall. These are avoidable accidents.

When we recall that there are such conditions as hemophilia, the lymphatic diathesia, kidney, heart, and lung affections, and that operating on patients suffering from these things may easily result in death, the importance of a careful preoperative examination of the general condition of the patient is apparent. Death following an operation for abscess of the brain, extensive carcinoma, suppurative peritonitis, or any other condition in which the operative procedure is a forlorn hope, while unfortunate and to be regretted, does not necessarily cast upon the surgeon even a shadow of carelessness or incompetency. But to take a child in apparent health and to subject it to a tonsillar operation, and then have to face a fatal issue, is a most deplorable experience. We as medical practitioners must see to it that such a death cannot in any way be associated with a lack of appreciation of such a possibility or a lack of precaution both before, during, and after the operation.

ACHYLIA GASTRICA.

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Achylia gastrica we understand to be a condition which manifests itself clinically by a persistent absence of free as well as combined hydrochloric acid and also by the absence of gastric ferments.

The total acidity after an Ewald test breakfast is below 10 and after a Leube-Riegel test-meal it may reach as high as 20. In other words we are dealing in achylia gastrica with a complete loss of one of the main functions of the stomach—namely, with that of digestive secretions.

Einhorn[1] was the first to name this disease achylia gastrica. He advanced at the same time the theory that the affection is neuropathic, based on his numerous clinical observations that the gastric contents while showing the absence of active secretions failed to show any pathological evidence of gland destruction.

Martius[2] was likewise of the opinion that achylia gastrica is a neuropathic disturbance of gastric secretions, but he considered it to be in the majority of cases of congenital origin. Different authors (Albu[3] and others) upheld Martius by showing that the disease is not so rare in childhood.

Ewald,[4] who called the affection anadeny gastrica, was of the opinion that it is the atrophy of the gastric glands that causes the achylia.

L. Kuttner,[5] a pupil of Ewald, is so firmly of the belief that achylia gastrica is only the result of a complete disappearance of the gastric glands that he goes so far as to assert that achylia gastrica is a progressive stage of gastritis anacida; in fact, he wishes to have the name gastritis anacida replace the term achylia gastrica. He bases his assertions on the postmortem findings by himself and his pupil Lindeman, whose cases were typical of gastritis with disappearance of the digestive glands. Kuttner also states emphatically that the fact that Einhorn and others found no evidences of pathological changes in the stomach contents of diseased mucous membrane or glands is no proof that there is no disease existing. Kuttner rightfully claims there may exist a pathological condition in the mucous

[1] New York Med. Press, September, 1888; New York Med. Record, June, 1892; New York med. Wchnschr., July, 1892; New York Med. Record, June, 1894; Arch. f. Verdauungski., vol. i, No. 2.

[2] Achylia Gastrica, 1897.

[3] Berl. klin. Wchnschr., 1903, No. 41.

[4] Berl. klin. Wchnschr., 1892, Nos. 26 and 27.

[5] Krauss-Brugsch: Spec. Pat. and Ther. Innerer Krank., 1914, v, pp. 6–14.

membrane without the stomach contents showing any evidence thereof.

The controversial views outlined above, coming as they do from very reliable sources, prove to us that achylia gastrica may really exist under manifold pathological conditions. In order to make clear the exact underlying cause of achylia and its clinical significance a short review of the physiology of gastric secretions and the factors that govern them is essential.

Exact studies of the physiology of gastric secretions have become possible chiefly through the ingenious studies of Pawlow[6] and his pupils, O. Cohnheim,[7] Richet,[8] Bickel,[9] Cannon, Carlson, F. Umber,[10] Pfanndler,[11] H. Strauss[12] and others.

Gastric juice is almost exclusively secreted in the fundus part of the stomach, the chief cells yielding pepsin and the parietal cells HCl. O. Cohnheim showed that these glands possess a nervous mechanism of their own. Direct mechanical or electrical irritation does not excite secretions in the stomach. On the other hand the sight of food, chewing, or smelling does excite gastric secretion, showing that psychical and reflex influences play an important role in bringing about gastric secretions. Such secretions induced by the sight of food is termed by Pawlow psychical juice; if produced by chewing it has been termed by Bickel appetite juice.

When food reaches the stomach four to six minutes elapse before secretions set in, but it meets there a secretion already possessing digestive properties and serving the purpose of chymification. Bickel demonstrated that the products of the earliest part of digestion are partially absorbed, thus stimulating the secretory and motor apparatus of the stomach.

To study gastric juices in man it is customary to give the patient a standard meal to be removed from the stomach after a definite length of time. After an Ewald test breakfast (250 grams weak tea without sugar and 50 grams white bread) Boas gives the approximate acidity figure of 0.07 to 0.2 free acid and a total acidity of 30 to 70 per cent.; after a test meal (150 grams beef, some potatoes, a plate of soup, and bread) free HCl 0.15 to 0.2 and a total acidity 75 to 87 per cent.

Pure gastric juice as obtained from a dog through the well-known experiments of Pawlow and from human beings with gastrostomy and esophagostomy (Richet, Bickel), or such as was obtained from gastrostomy patients (Umber, Carlson, Bickel), shows 0.4 to 0.5 free HCl and 100 to 140 per cent. total acidity.

[6] Die Arbeiten d. Verdauungsdrüsen, Wiesbaden, 98.
[7] Die Physiolog. d. Verdauungski. u. Ernah., Wien, 1908.
[8] Jour. de l'Anat. et Physiol., 1887.
[9] Berl. klin. Wchnschr., 1905, p. 60; München. med. Wchnschr., 1906, x, 1323; Int. Beitr. zur Path. u. Ther. d. Ernah., 1913, lxxv.
[10] Berl. klin. Wchnschr., 1905, No. 3.
[11] Arch. klin. Med., 1900, xv, 255. [12] Berl. klin. Wchnschr., 1893, p. 398.

In gastrostomized dogs and human beings with gastric fistula it was found that disgust, anger, or fright stop gastric secretions. On the other hand the sight or smell of appetizing food or pleasing influences increase gastric secretions. Bickel found that nicotin retards gastric secretion. H. Strauss demonstrated that fats and Schuele that concentrated salt and cane-sugar solution have a retarding influence on gastric secretion. Meat juices, CO_2, alcohol, diluted sodium chloride solutions, and local heat excite gastric secretions. Most of the amara (extr. fluid colombo, extr. fluid condurang., etc.) were found by A. J. Carlson, contrary to previous belief, to retard gastric secretions.

The average quantity of gastric juice secreted in the course of the day has been calculated to amount to 1500 c.c. The acidity values take a definite course by a reflex mechanism, whereby the acidity rises gradually, reaching the highest point at the height of digestion, and gradually declining, reaching the lowest point when the stomach is empty.

Recent studies were made by Rehfuss, Bergheim, and Hawk[13] of gastric secretions by the so-called fractional method. This consists of introducing a thin weighted tube into the stomach based on the principle of the Gross duodenal tube, after an Ewald test breakfast, and aspirating every fifteen minutes, thereby studying the secretory curve. Similar work was carried on by Max Skaller[14] in Bickel's laboratory in Berlin. They found that even in health the secretory curves vary; they accordingly describe three curves:

1. The isosecretory curve, the height of secretion having a total acidity of 60 per cent., maintaining such acidity for from thirty to sixty minutes, after which it gradually declines. After two to two and a half hours there is a complete disappearance of food residue.

2. The hypersecretory type shows a rapid response to stimuli. Aspiration of contents after five minutes may show an already high total acidity. The highest is 100 per cent. with a gradual decline, and although the food has completely disappeared after two to two and a half hours there still is an outpouring of pure gastric juice for a long time thereafter.

3. The hyposecretory type, wihch is characterized by a slower ascend, a slower response to stimuli, and a high point of from 40 to 50 per cent. total acidity.

Of paramount importance to the physiology of gastric secretions are the numerous experimental studies of A. J. Carlson,[15] on his subject Mr. V., with a complete closure of the esophagus and a gastric fistula. He found, in contradiction to Pawlow, Bickel, and Schuele that the gastric secretions are continuous and only the quantity of the secretion differs according to the time of day and season. In

[13] Jour. Am. Med. Assn., 1914, lxiii, 909; Am. Jour. Med. Sc., 1914, p. 848.
[14] Berl. klin. Wchnschr., 1913.
[15] Am. Jour. Physiol., 1915, xxxvii, 50. Ibid., 1915, xxxviii, 245.

the morning, on a fasting stomach, the quantity is greater than before lunch or dinner, and more in the summer than in winter. He attributes this change in quantity to the tone in the stomach. Be the quantity of secretion whatever it may it always contains pepsin and a varying degree of HCl. This continuous secretion is, according to Carlson, supposed to be due either to the continuous action of the vagus on the secretory glands or to an autodigestion of the gastric juice.

Another important point brought out by Carlson, confirming the work of Pawlow and Boldyreff,[16] is that the acid concentration of gastric secretion is always the same. The higher or lower acidity obtained from a gastric fistula or through the stomach-tube depends, according to Pawlow, on the mucous secretion in the stomach, and according to Boldyreff and Carlson to the regurgitation of intestinal juice.

Gastric juice has a digestive action on proteids, converting them into peptones and polypeploids; according to Ad. Schmidt it also acts on connective tissue. O. Cohnheim says the HCl also prevents bacterial growth in the stomach, fermentation, and decomposition. Finally, HCl regulates the action of the pylorus.[17]

Normal gastric secretions are kept up by the integrity of the gastric glands, the healthy condition of the blood, and the proper control of the nerves. Disturbances in digestive secretion result when any one of these three factors is at fault.

In relation to achylia gastrica it needs no explanation that an atrophy of the secretory glands of the stomach or a marked pathological change of the blood can be a causative factor. The mode by which a purely functional disturbance of the nervous system may cause a lasting achylia, as asserted by Einhorn, needs a short discussion of the nerves directly influencing gastric secretion. This was made possible by the physiological studies of Langley[18] of the vagus-sympaticus system; the pharmacological studies of Meyer and Gottlieb[19] and the clinical observations of Eppinger and Hess[20] on the same system.

It would be out of place here to go into a detailed anatomical description of the vagosympaticus, but a few remarks on the influence of these nerves on gastric secretion are essential in order to understand how a functional disease of the nervous system can be made responsible for achylia gastrica.

It was Langley who showed that all the organs not controlled by the will (stomach, intestines, bloodvessels, ducts of glands) and also certain organs possessed of striated muscle fibers (the heart, the

[16] Quart. Jour. Exp. Physiol., 1914, viii, 1.

[17] v. Mehrinz: XII Kongr. f. inner. Med., 1893, p. 471. Hirsch: Zentralbl. f. klin. Med., 1892, p. 993; 1893, xiv, 73, 377, 601.

[18] Jour. Physiol., 1898, xxiii, 240; 1911–12, xliii, 173.

[19] Experiment. Pharmacol., Vienna, 1912.

[20] Zur Path. d. Veget. Nerven-System, Ztschr. f. klin. Med., lxvii lxviii, 205, 345.

beginning and terminal portions of the alimentary canal, and the generative organs) are under the control of the vagus and sympaticus system. It was also shown and pharmacologically demonstrated by Meyer and Gottlieb that these two systems antagonize each other throughout the greater extent of their course.

In reference to gastric secretions, which concern us here most, it was shown that the vagus excites secretions and the sympaticus inhabits secretions. Atropin, for example, paralyzes the vagus, thereby causing a cessation of gastric secretions; pylocarpin, on the other hand, stimulates the vagus, thereby causing an increase in gastric secretions. Adrenalin stimulates the sympaticus and so inhibits gastric secretions. Eppinger and Hess succeeded in demonstrating in the human being characteristic manifestations indicating functional disturbance in either the vagus or sympaticus, or both. Individuals with an increased tone in the vagus system they termed vagotoniacs, while those with increased tone in the sympaticus are named sympaticotoniacs. They also showed that there exist clinical evidences of an increased vagus action in vagotoniacs (contracted pupils, increased salivation, slow heart, increased gastro-intestinal secretions), and an increased sympathetic stimulation in sympaticotoniacs (dilated pupils, dry mouth, flushed face, and diminished gastric secretions).

Not all symptoms have to be present in order to stamp one as a vagotoniac or sympaticotoniac. There are numerous cases in which certain organs show signs of vagotonia and other organs again signs of sympaticotonia. For example, the heart's action may give the signs of a vagotoniac's slowness, respiratory arrhythmia, while the stomach shows signs of sympaticotonia (diminished or absent secretions).

It was Eppinger and Hess again who showed that individuals with a disturbance in either of the above-named systems only demonstrate the condition after the administration of drugs influencing either system. Pilocarpin even in smallest doses provokes vagus symptoms, while adrenalin in equally small doses provokes sympaticus symptoms.

In achylia gastrica it is plausible to assume that there is an inborn or an acquired sympaticotonia. It is very probable that the same patients who have during middle life achylia gastrica on the basis of sympaticotonia may have had in their earlier years hypersecretions on a vagotonia basis. Einhorn rightfully expressed the view that the finding of atrophy of the gastric glands in a prolonged case of functional achylia gastrica is due to inactivity of the glands (disuse atrophy). Knowing through the proved studies of von Bergman[21] and his pupils, J. Kauffman,[22] and our own observations[23] that the

[21] München. med. Wchnschr., 1913, No. 4, p. 169.
[22] Ztschr. f. klin. Med., 1914.
[23] Arch. Int. Med., March, 1914.

hypersecretion accompanying vagotonia may eventually lead to pathological changes in the gastric mucosa (ulcus ventriculi) it is reasonable to assume that a prolonged sympaticotonia inhibiting gastric secretions would eventually lead to atrophy of the gastric glands.

ETIOLOGY. The above discussion would lead us to divide achylia gastrica from the etiological stand-point into three groups:

1. Achylia gastrica with destruction of gastric glands either on the basis of chronic, progressive gastritis (Kuttner), or carcinoma, linitis plastica, alcoholic gastritis with cirrhosis of the liver (Lockwood).

2. Achylia gastrica accompanying marked secondary and primary anemias. To this group belongs the achylia of primary pernicious anemia; the marked anemias accompanying tape-worm; the lowered acidity and even achylia in syphilis as well as the achylia described in chronic rheumatism, gout, hyperthyroidism, etc.

Gravitz was of the opinion that pernicious anemia is secondary to toxins developing as the result of the gastro-intestinal disturbance, especially when accompanied by achylia gastrica. Sahli is likewise of the opinion that pernicious anemia is secondary to achylia gastrica because in the absence of HCl the iron is not assimilated.

From the clinical observations, we agree with the authors who make the anemia responsible for the achylia and not the achylia responsible for the anemia.

3. Achylia gastrica of a functional nature. To this group belong the great majority of cases in whom there is a demonstrable disturbance of the vagosympaticus system with a predominating sympaticotonia of the gastric secretion.

Disqué[24] pointed out that these patients either present the type of status asthenicus (Stiller) or that of the status apoplecticus. In the status asthenicus one usually meets with the mixed type (vagosympathicotoniac), while in the apoplectic type the sympaticotonia may predominate throughout the entire system. The not infrequent occurrence of achylia during the menopause as well as the achylia in Addison's disease show the relation of the sympathetic disturbance to the absence of gastric secretion.

The achylia gastrica secondary to gall-stones and appendicitis or other intra-abdominal diseases as pointed out by Lockwood[25] are also in most cases based on a sympaticotonia. The disease in one of the intra-abdominal organs only serves as an exciting factor in bringing about the manifestations of sympaticus disturbance. This is also the reason why the removal of the cause improves even the gastric secretions.

The interesting experimental work of Carlson and Keenton[26] showed that the removal of the parathyroids produce achylia which is remedied by the administration of calcium.

[24] Arch. f. Verd., 1914, xx, 366.
[25] Diseases of the Stomach, 1913.
[26] Am. Jour. Phye., 1914, xxxiii, 25.

Morbid Anatomy. In the functional type of achylia gastrica the gastric mucosa will in the majority of cases not show any macroscopic or microscopic changes in the gastric mucosa.

Only rarely will moderate atrophic changes of the gastric mucosa and secretory glands be met with secondary to inactivity of the glands (disuse atrophy). In the organic type of achylia gastrica partial or complete disappearance of the gastric mucosa is seen with the naked eye. Microscopically various stages of destruction of mucous membrane and glands are seen, such as fatty and cystic degeneration of the glands and atrophy of the mucosa. Cylindrical epithelia frequently assume the shape of goblet cells; rarely the pathological changes are seen to have penetrated the submucosa, muscularis, and serosa.

Age. The affection is most common after the age of forty. Individual cases in earlier life are reported. This affection is much more frequent in men than in women. It is sometimes met with in diabetes, gout, etc., bad teeth are a predisposing factor.

Symptoms. The symptoms of achylia gastrica either on an organic basis or secondary to marked anemia are treated when discussing differential diagnosis between the functional achylia gastrica and the above-named affections. Here only the symptoms pertaining to functional achylia gastrica are being considered.

In a fair number of cases the disease gives rise to no symptoms whatsoever.

There is another class of cases in which diarrhea is the only symptom. Here the stools contain even macroscopically muscle fibers and connective tissue, and are erroneously treated for intestinal disease when in reality the examination of the stomach contents discloses the achylia to be the causative factor for diarrhea, one form of gastrogenic diarrhea.

Another group of cases of achylia have vague gastric disturbances, fulness after meals, nausea, belching, bad taste, and marked dryness in the mouth, etc.

In a small number of cases the symptoms occur periodically with severe epigastric pains, nausea, sometimes even vomiting. The pains are independent of meals, spreading over the entire upper quadrant of the abdomen and radiating to the back. Adolph Schmidt has termed such cases achylia dolorosa. There may be considerable burning in the stomach not relieved by food or bicarbonate of soda. The tongue is coated and appetite is lost. It has even been found that erosions with fatal parenchymatous bleeding resulted in late stages of achylia gastrica. Such bleeding was explained as being due to erosions caused by regurgitated trypsin into the stomach.

O. Gross[27] describes cases of achylia gastrica associated with

[27] München. med. Wchnschr., 1912.

symptoms pointing toward pancreatic disturbance (bulky, fatty stools, containing an increase in fat, muscle fibers, and starch, and a diminution of the pancreatic ferments in the duodenal contents and stools). He has termed such cases achylia pancreatica. This form of achylia is rare. Whether achylia pancreatica is an independent affection, as O. Gross assumes, or is secondary to a long-standing achylia gastrica, is not definitely settled. Be the symptoms what they may it is characteristic of the functional type of achylia gastrica, that there are very marked intermissions of well-being and that the long duration of the disease does not interfere with the general appearance of the patient. A great majority of these cases even increase in weight notwithstanding their complaints.

Diagnosis. This is chiefly based on the examination of the stomach contents and the stools. From the fasting stomach we can neither by expression nor by aspiration obtain any contents. Lavaging such an empty stomach one obtains pure wash-water in the greater number of cases; in a lesser number mucus of normal macroscopic and microscopic appearance is found. In the smallest number of cases evidence of an inflammatory condition of the mucous membrane and destruction of glands is seen, such as increase in cellular elements and atrophic appearance of the glands.

To draw diagnostic conclusions from pieces of mucous membrane obtained by aspiration or lavage of the stomach must be employed with care, because fragments of mucous membrane are present even normally as a result of the trauma caused by the aspiration. In achylia, aspiration more readily causes pieces of mucous membrane to become separated because of the existing vulnerability in the gastric mucosa.

The non-finding of particles of mucous membrane does not exclude a pathological change in the lining of the stomach. Only the constant presence of pieces of mucous membrane in the stomach content, showing microscopically destructive changes indicates a diseased condition of the gastric mucosa. This is, however, the exception in the achylia gastrica described by Einhorn and Martius and is regularly found in that form of achylia which is a progressive stage of gastritis subacida (anadeny gastrica, Ewald) and the achylia resulting from diseases of metabolism and blood.

The stomach contents obtained seven or eight hours after a Bourget-Faber test meal (250 c.c. barley soup, 2 slices of bread, 50 grams chopped meat, and 8 prunes) have, according to Kuttner and Lindeman, shown a residue of prune shells. They conclude from this there is a diminished motility in certain cases. This is, however, a hasty conclusion as to the judgment of motility in achylia because the remnant of pieces of prune shells in achylia are more likely due to the fact that the shells stick to the gastric wall because of the absence of fluid.

The removal of the stomach contents one hour after Ewald's test

breakfast shows the food to be unchanged, just as if it had only been chewed and only a very small quantity of light fluid flows on top. The food mass shows partially to be interwoven with some mucus. At times no food is obtained one hour after Ewald's test breakfast because of the open pylorus. In such cases we must remove the contents three-quarters or even half an hour after the test breakfast. Such stomach contents are usually entirely devoid of odor, contain no free acid and no combined acids. The total acidity is below 10. Important is the absence of ferments. We must, however, not be satisfied with the diagnosis until a Leube-Riegel meal (400 c.c. meat soup, 150 to 200 grams beefsteak, 150 grams mashed potatoes) is taken by the patient and the stomach contents removed between two and a half and three and a half hours (at the height of digestion). If then no free and combined acids, a low total acidity, and absence of ferments are found the diagnosis is certain. An additional aid in diagnosis has been furnished by Rehfuss and his coworkers by the fractional method of examining stomach contents as described above.

In achylia gastrica we accordingly employ the Gross duodenal tube, and introducing it 50 cm. leave it there for hours, aspirating from time to time. The gastric juice obtained throughout the entire procedure fails to show the presence of free or combined acids. If by the fractional method acid is obtained in the course of digestion one deals with a subacidity or gastritis anacida but not the functional achylia.

Jaworski determines the presence of achylia in the following manner: He gives his patient 300 to 400 c.c. of dilute HCl half an hour before the test breakfast. The contents removed three-quarters to an hour later must show no free or combined acid if there is a true achylia. The examination of the stools may frequently show muscle fiber and free connective tissue. This is particularly marked when diarrhea is present, but even in constipation while connective tissue is not so frequent, muscle fibers are found.

When the disease progresses so that the external secretion of the pancreas is likewise disturbed, fat and starch as well as the diminution of trypsin, amylopsin, and steapsin are found in the duodenal contents and the stools. A diagnostic aid is furnished by Schmidt's test-meal, consisting chiefly of 100 grams of chopped beef half rare. Normally, none or but very few shreds of connective tissue are found microscopically in the stool, while in achylia connective tissue is found in abundance. It must be emphasized that a perfectly normal stool without any evidences of disturbed digestion does not exclude the existence of achylia.

The mode of filling and emptying of the stomach in achylia gastrica as in all gastric affections can best be studied by means of the roentgen ray. The filling of such a stomach, as first pointed out by Holzknecht, is slow. One sees the contrast food stop for thirty seconds or one minute below the air bag, and the food dribbles down

to the lower part of the stomach likewise very slowly. This is attributed to the dryness of the stomach wall.

While this explanation sounds plausible it does not completely satisfy our reasoning that the dryness in the stomach alone should account for the slow filling of the cardiac end of the stomach. It appears to us that the slow filling is rather due to the fact that the air bag (magenblase) is much larger in achylia, thereby interfering with the action of the diaphragm, which, according to Cannon, is so important in filling the cardiac end of the stomach with food and furthering it toward the pyloric end.

Peristalsis of the stomach in achylia differs from the normal in the following manner: normally when the first few morsels of food reach the lower pole of the stomach one sees at once a peristaltic wave in the region of the pylorus, sometimes resulting in antrum formation, although but very little or no food at all passes the pylorus. As the stomach fills up completely with food, peristalsis ceases for four or five minutes, when it is again resumed in its normal manner. It begins at a point just opposite the incisura cardiaca running along the greater curvature forming shallow waves. At a point oppsite the incisura angularis the waves deepen finally, forming an antrum. Very small waves are also seen along the lesser curvature.

To recapitulate, we have a period of peristaltic waves in the region of the pylorus corresponding to the gastric secretion met with by the first morsels of food, brought about reflexly by the act of chewing and deglutition. This peristaltic action may be termed the initial period of peristalsis. Then comes the period of filling and strata formation in the stomach when no peristalsis occurs. This may be termed the period of latency. After four to six minutes, corresponding to the time of the real setting in of secretion, the regular course of contraction waves begins.

In achylia gastrica, on the other hand, because of the absence of secretions, the initial peristaltic wave is absolutely missing. The period of latency is unusually prolonged, and when contraction waves begin they are very superficial. We see, therefore, that the roentgen ray observation in relation to peristalsis of the stomach fully confirms the physiological teaching—that peristalsis of the stomach is primarily dependent to a great extent on the secretions. The superficial peristalsis in achylia gastrica is brought about by the mechanical influence of the food.

The emptying of the stomach is unusually rapid in achylia gastrica; because of the absence of the acid reflex, the pylorus is open. This rapid emptying is also present in the great majority of cases in the small intestine, and in a goodly number of cases there is also hypomotility of the colon (achylic diarrhea).

Differential Diagnosis. The diseases from which achylia gastrica is to be differentiated are: gastritis anacida, syphilis of the stomach, carcinoma ventriculi, and heterochylia (Hemmeter).

From gastritis anacida achylia is differentiated by the absence of

mucus, the complete absence of ferments, and the non-return of acids by food stimulating secretions or by the giving of dilute HCl before meals (Jaworski). Furthermore, the gastritis anacida has mostly a higher total acidity, and constipation is by far more common than in achylia.

To differentiate achylia gastrica from carcinoma is especially difficult in cases in which achylia is associated with epigastric pains or with a severe anemia. Here all clinical methods helping to establish a diagnosis must be resorted to. The important points are: the higher total acidity in carcinoma, the presence of considerable mucus, an increase in free leukocytes; if stagnation is present we find lactic acid and Boas-Oppler bacilli. In cases in which the carcinoma ulcerates we may succeed in finding cancer cells in the washed-out stomach contents. P. Cohnheim found characteristic flagelli in carcinoma. The persistent finding of occult blood in the stool speaks for carcinoma.

The careful laboratory tests, such as that of Wolf-Junghans, the improved method of staining, the Boas-Oppler bacilli, the formol index, and the glyeyltryptophan test,[28] have yielded in a high percentage of cases such valuable results in differentiating carcinoma of the stomach from achylia that it is well worth our efforts to carry out these tests with as much exactness as employed by Smithies.

In the Wolf-Junghans test the patient gets at 4 P.M. on the day previous to the examination one ounce of castor oil. At 6 P.M. of the same day a mixed meal is taken and at 7 P.M. 20 seedless raisins. The following morning the gastric contents are aspirated and lavaged in order to determine whether the stomach is really empty; 200 c.c. of water and 60 grams of two-day old white bread is taken by the patient and removed between fifty and sixty minutes later. The contents are filtered through double HCl-washed filter paper, and the filtrate is first treated for albumin within one hour after removal and then in the following manner.

Into six test-tubes, each of a capacity of 20 c.c., we put stomach contents of $1, \frac{1}{2}, \frac{1}{4}, \frac{1}{10}, \frac{1}{20}, \frac{1}{40}$, c.c. respectively. To each tube enough distilled water is added to make a total of 10 c.c. This furnishes us therefore the following dilutions of the stomach contents:

Tube 1 equals $\frac{1}{10}$.
2 " $\frac{1}{20}$.
3 " $\frac{1}{40}$.
4 " $\frac{1}{100}$.
5 " $\frac{1}{200}$.
6 " $\frac{1}{400}$.

To each of the tubes we now add 1 c.c. of the following solution:

Phosphotungstic acid	3 c.c.
HCl (concentrated)	10 c.c.
Alcohol (96 per cent.)	200 c.c.
Aqua dest.	ad 2000

[28] F. Smithies: Carcinoma of the Stomach, Smithies and Ochsner, Saunders, 1916.

If the pearly white zone appears also in the fourth tube the case arouses suspicions of cancer; if in the fifth and sixth tubes we call the result positive.

For finding the Boas-Oppler bacilli Smithies employs the so-called colored agar stain for the gastric extracts, which is made as follows:

Prepare a 2 per cent. solution of agar in distilled water. While the solution is still hot filter through double HCl-washed filter paper a few times. Then fractionally sterilize and filter for three consecutive days. Pour 5 c.c. of this solution into test-tubes and plug with sterile cotton.

The stains comprise the following: Unna's polychrome methylene blue and fresh Lugol mixture.

The test is performed thus: Liquefy the contents of one of the test-tubes and divide this into two. To each add 15 drops of stain—the methylene blue to one and the Lugol solution to the other. Mix the contents well and place the tubes in a beaker of boiling water. Now make thin smears of the gastric extracts on two separate slides. Fix these. To each of these add one drop of the staining mixture (the Lugol stain to one and the methylene blue to the other) and drop a cover-slip on each of the preparations. Wait one minute (while the preparations are fixing) and examine microscopically. By this method the Boas-Oppler bacilli stain blue and the starch, etc., is stained brown by the Lugol solution.

Glycyl tryptophan test: Prepare 10 test-tubes, each containing 0.5 c.c. glycyl tryptophan. Add to each 5 c.c. of filtered gastric juice. Then make two additional control tubes, one containing 0.5 c.c. glycyl tryptophan and 5 c.c. of normal saline, the other containing only 5 c.c. of normal saline. To each of the twelve tubes add 0.5 c.c. of toluene, invert the tubes several times and incubate for twenty-four hours at 37° C.

Now have ten clean test-tubes ready. Into each tube introduce 2 c.c. of the mixture below the toluene. To each of these add 3 drops of glacial acetic acid (3 per cent.). Shake tubes well. Then allow bromine vapors to flow into each tube until an amber-yellow color appears. Shake the tubes again. Examine by daylight. A rose-pink color indicates a positive reaction.

Formol Index. This test depends on the property of gastric juice from stomach cancers to split peptone into the amino-acids. Hence there is an ereptic enzyme in the stomach contents in this disease. We determine the presence of this enzyme by the amount of amino-acids found (by titration with decinormal sodium hydroxide to phenolphthalein) after treating peptone solution with the suspected gastric contents. The test is performed as follows:

Into a test-tube 20 c.c. of filtered Witte's peptone solution (5 per cent.) and 1 c.c. of filtered gastric juice are introduced. Now three control tubes are prepared, one containing the above plus 10 c.c. of decinormal sodium hydroxide, another containing 20 c.c. of

the peptone plus 10 c.c. of the decinormal sodium hydroxide, and the third containing the 20 c.c. peptone alone. To each of the four test-tubes 1 to 2 c.c. of toluene is added (to prevent putrefaction) and are incubated for twenty-four hours at 37° C. Then 10 c.c. of 40 per cent. formaldehyde which has been treated in the following way is added to each. The formaldehyde is neutralized with sodium hydroxide to 0.5 c.c. of phenolphthalein (0.5 per cent. in a 50 per cent. alcohol solution).

Now titrate each tube immediately and in gastric cancer one finds in the first tube an acidity equivalent to 20 c.c. and above of the alkali, in ulcus carcinomatosus 19.8 c.c., in cancer of the liver 4 c.c., in gastric ulcer 12, and in achylia 14.

The different biological tests to facilitate the diagnosis of carcinoma as well as the increase of pepsin in the urine, while scientifically interesting, have not aided in the diagnosis of carcinoma. A great aid in the differential diagnosis is furnished by the roentgen ray, and in a very great majority of cases of carcinoma of the stomach it will supply a clue.

Advanced stages of carcinoma of the stomach show such outspoken changes that a description is not here deemed essential. Only such cases of carcinoma of the stomach will be discussed the structural changes of which are not so marked, and where, unless a very careful roentgenological study is exercised, diagnosis would be impossible. In studying such cases, as in achylia gastrica the mode of filling, peristaltic action, appearance of stomach, and mode of emptying are to be considered. The roentgen ray characteristics of achylia gastrica have been mentioned above.

In carcinoma even in early stages there is a tendency to atony of the stomach so that the food drops down, distending the stomach like a bag. If there is even moderate involvement of the pylorus one sees it fill very slowly, being passively distended, as it were, by the food, unlike the normal pylorus which fills in a ball-like manner, showing visible peristalsis. Peristalsis is persistently absent in that part of the stomach infiltrated by carcinoma, so that the straight, rigid, and transversely stretched-out lesser curvature with absent peristalsis speaks, as well pointed out by Levy-Dorn and Ziegler, for early carcinoma of the lesser curvature. The rigid, elongated, tube-like pylorus indicates early cancer of the pylorus.

The appearance of the stomach is practically as described above—bag-shaped with absence of peristalsis in the affected areas, and usually a dextra-position with a tendency to the bull-horn shape of the stomach, the pylorus forming persistantly the most depending portion. The emptying of the stomach due to the open pylorus is hastened, and at no time does one see the contractile action of the pylorus. Should the carcinoma of the pylorus have reached a size to offer a partial obstruction to the passage of food we find no change in the mode of emptying in the first part of digestion, but a residue is

present six hours after the meal, although the rest of the contrast substance already fills the entire colon down to the rectum.

A form of carcinoma of the stomach that gives the same clinical symptoms as achylia in the absence of palpatory finding occurs in complete scirrhous involvement of the stomach. In such cases the roentgen ray is of inestimable value. It represents an elongated transversely situated tube-like organ lying high in the abdominal cavity, which is seen to serve only as a passage-way for the food. A similar picture is also presented by linitis plastica.

It must be stated, with emphasis, that there are cases in which a differential diagnosis between achylia gastrica and carcinoma is impossible by means of the roentgen ray. These are the cases in which the posterior wall of the stomach alone is involved.

In a certain number of cases, as pointed out by Th. Hausman,[29] achylia gastrica with all the clinical symptoms results on the basis of syphilis. Here the Wassermann reaction and the Noguchi-Luebin reaction will aid a great deal. The importance of the Noguchi-Luebin reaction in syphilitic affections of the stomach is confirmed by F. Smithies[30] in a large number of cases.

It still remains for us to differentiate achylia gastrica resulting on the basis of secondary or primary anemias. The achylias resulting from secondary anemia are determined by establishing the etiological factor (intestinal parasites, metallic poisoning, gout, diabetes, etc.). More important to differentiate is that form of achylia associated with primary pernicious anemia. In these cases a real anadeny exists. The blood picture is the most important diagnostic aid, inasmuch as it shows that we are dealing in the anemia with a hemolytic disease and not with one of digestive disorder. The leading points are: high color index; poly- and hyperchromatic condition of the red blood cells; leukopenia; diminution or absence of blood platelets; diminution of resistance of red blood cells. The work of Eppinger as well as that of J. P. Schneider[31] demonstrating urobilinogen and urobilin. In the chocolate-colored duodenal contents will also serve to demonstrate that the achylia gastrica is secondary to the anemia.

In the diagnosis of achylia we must not overlook the differential diagnosis between it and heterochylia (Hemmeter[32]). By heterochylia we understand a condition in which the gastric secretions show a great tendency to changes in value of acidity. One examination may show a complete achylia and another examination, after a shorter or longer interval, may show even a hyperacidity.

If we meet with a heterochylia during the state of achylia and

[29] Ergebn. f. inner. Med. im. Kinderheilkund., 1911, vi, 279. Th. Brougsch and Schneider, Berl. klin. Wchnschr., 1915, p. 601.
[30] Arch. Int. Med., January, 1916.
[31] Jour. Am. Med. Assn., August 14, 1915.
[32] Diseases of the Stomach, 1902.

examine the stomach contents of the same patient a few weeks later and find a normal or even a higher acidity we may be misled to attribute the change to the therapeutic effect. The mode of clearing up the differential diagnosis is subject to time. Heterochylia, as pointed out by Hemmeter, shows changes in the acidity values, and the patient has corresponding complains.

Complications. The most important complication is a resulting organic disturbance of the intestines. The primary diarrhea because of the existing hypermotility in the small and large intestine may eventually lead to fermentative diarrhea and later to catarrh of the small and large intestine.

A rare complication is brought about by the absorption in the blood of toxic proteins, the result of the loss of vicarious digestion on the part of the small intestines. Anaphylactic phenomena and gastro-intestinal disturbances grouped by Vaughn as protiosis occur.

Some authors claim that carcinoma may arise on the basis of an achylia. Pernicious anemia, claimed by Grawitz and others to be the result of achylia, does not seem plausible. As already stated above it is rather to be assumed that the achylia is the result of pernicious anemia.

PROGNOSIS. In the functional achylia gastrica prognosis as to life is favorable; the majority of patients even enjoy fairly good health throughout the greater part of their lives. Prognosis as to recovery to normal is unfavorable. Very few cases are reported in which gastric secretions have returned. Achylia gastrica on the basis of lues has a more favorable prognosis as to the return of secretions according to Brugsch and Schneider. According to Lockwood, cases of achylia associated with gall-stones and appendicitis are improved on the removal of the cause.

TREATMENT. Treatment must be strictly individualized, and for the sake of clearness, cases should be separated from the therapeutic stand-point into the following groups:

1. When the symptoms point to a general neurosis with corresponding gastric symptoms. The discovery of achylia in such patients must not lead us to believe that the cause of nervousness has been discovered and that the proper therapeutic measures against achylia will have a favorable influence on the nervous system. In the great majority of cases the reverse holds true. The achylia is the expression of a general neurosis and the treatment must therefore be directed against the nervous system with moderate and appropriate attention to the stomach. Such patients should lead a most regular life, both physically and mentally; they should avoid toxic agents like tobacco and excessive alcohol. Therapeutic measures should be employed, depending upon the general condition of the patient. Robust people should be advised to take once or twice a week some form of sweat bath (box bath or Turkish or electric bath), also a

morning shower. Weak people should take half-baths of 98° to 100° F. temperature with friction of the chest while in the bath and a cold towel on the head, the procedure to last from ten to fifteen minutes, after which water of lower temperature, 90°, is to be poured over the spine. With some patients the cool pack for from a half to an hour is more effective. When the patient can afford frequent and short vacations, either seashore or mountains are very beneficial. For the gastric symptoms a spa containing the sodium chloride waters (Saratoga, Hot Springs, Kissingen, Homburg, Dresden, Tarasp) for one month is very beneficial. In choosing such a spa it is essential to call the attention of the local medical adviser to the existing neurosis so that not the drinking of the waters shall play the main role, nor even the diet, but the general measures to tone up the nervous system shall be of prime importance.

The dietetic régime should not be so strict as to make the patient everlastingly dependent. In a general way we direct him to reduce the daily quantity of meat. He must be told to chew his food well. In this affection thorough chewing almost to the extent of Fletcherizing is of the utmost importance, for as the pylorus is open and as the food passes through the stomach quickly, poorly chewed food serves as an irritant to the small intestine. It is evident that proper attention should be paid to the teeth. Spices in moderation are beneficial (pepper, also cinnamon, salt, caviar, vanilla, orange peel, etc.). Of the liquors a light sour wine with the meals is useful. Lemonade, Billiner waters, Saratoga sparkling water, and sour drinks are preferable to plain water.

To the second group belong cases in which the gastric symptoms predominate (continuous burning right after meals, pressure, and even pain). The symptoms may be so distressing and persistent, and, due to the fear of eating, even cause some loss of weight, that an understanding of the exact nature of the disease is most trying. Lockwood even goes so far as to state that these pains are of extragastric origin (cholelithiasis, appendicitis) and that the removal of the cause would cure the achylia. This does not correspond to our experience. We are rather inclined to think that the persistent and severe symptoms are likewise exaggerated because of the underlying neurosis. That removal of the extragastric disease improves the symptoms of achylia does not prove that this was the cause of the disease, because we know that neuropathic individuals often get well after an exploratory laparotomy, although nothing was found at the operation. All this is stated with the object of showing that while in this group of cases our dietitic and medicinal régime must be more carefully outlined, we must not lose sight of the psychical part of the treatment.

The diet must be guided according to the following principles: The food is prepared sufficiently so as not to be a burden to the intestines mechanically, and must also be of a nature to depend least

on stomach digestion and at the same time not to irritate the small intestine. It is best to divide the dietetic treatment into two parts—that of sparing the digestive organs and of exercising those organs. The sparing diet must be individualized as to the kind of food and the length of time such is to be carried out, depending on the severity of the symptoms. When these are very distressing it is necessary to keep the patient on warm milk, cream, and yolks of eggs for the first four or five days, then gradually progress to thin cereals prepared in milk, toast, and butter up to the end of the first week, during all of which time the patient should remain in bed. When the symptoms have considerably diminished we can add bouillon with egg, beef soup, and of the vegetables first mashed potatoes with butter, because they are best borne, then spinach, asparagus tops, string beans, etc., all passed through a purée sieve.

During the second week two or three eggs may be given daily, and the cereals in the form of light puddings or custard. If the patient is fairly comfortable in the second week, noodles and macaroni may be added to the diet. With meat we should begin gradually, and then only with finely scraped or chopped meat well done. Spices and alcoholic beverages should not be allowed while the acute symptoms last. When the symptoms are not of such a severe nature we can at once proceed with a diet corresponding to that described for the third week in the severe cases.

The exercise diet should not begin until the acute symptoms disappear, and even then not abruptly, so as to avoid a recurrence of symptoms, thereby undermining the self-dependence of the patient.

The following list is a fair and sufficient example of what an achylic patient should partake of and be fairly free from disturbance, and at the same time allow him enough variety. The dietetic mode of life for a great length of time of an achylic patient who is subject to gastric symptoms should be the following: In the morning, on an empty stomach, about three-quarters of an hour before breakfast 250 c.c. of hot water to which a half teaspoonful of Nachlorat is added. Breakfast: orange juice or grape fruit, then eggs in any form, with the exception of hard-boiled eggs, cocoa or light coffee or tea, Graham bread or rolls with butter. Two or three times a week we replace the eggs by cereals, mashed potatoes, noodles, macaroni, or cream cheese. Dinner: grape fruit or caviar or anchovies, sardines, sardelles as appetizers, then some bouillon or beef soup or well-prepared vegetable soup mildly spiced. Of the meats either fish, chicken, lamb, veal, or cooked ham, calf's brain, fresh sweetbread or even steak can be given, but thorough chewing is essential besides the proper preparation in the kitchen (well done and finely chopped and mildly spiced with onions, salt, and pepper). Of the vegetables, those named above and a cereal or noodle pudding or omelette, or prune soufflé and cooked fruits. At 4 P.M. one cup of buttermilk with zwieback or toast and butter. Supper: like break-

fast, with the addition of some cooked fruits, and buttermilk should replace the coffee.

Severe cases should rest in bed the first week and hot poultices should be applied to the abdomen. If these do not relieve the pain small doses of dionin (gr. 0.01) or pantopon (0.1), two or three times daily, may be given, and in order to secure a restful night, veronal (0.5) in suppositories or adalin (0.5) by mouth may have to be resorted to for a few nights. The bowels should be kept open by a daily salt enema or by an occasional dose of calomel (0.2) in one dose. Should marked nervous symptoms exist during that time a cool sponge bath or cool packs or, as a last resort, bromides in the form of atrontium or sodium bromides (0.6) twice a day may be given.

For bad taste in the mouth one should, besides the antiseptic mouth washes, have the patient use some pleasantly flavored chewing-gum or, as Schule advises, have him chew peppermint leaves, orange peel, or rhubarb root.

A bad taste in the mouth and distention are frequently remedied by a teaspoonful of rhubarb and soda, to be taken three times daily. If meteorism is a disturbing symptom an infusion of peppermint tea (1 to 250 c.c.), taken hot on retiring, is beneficial.

As improvement progresses a more liberal diet is partaken of, the amount of rest depending on the physical condition of the patient chiefly and to some extent also on circumstances. When the patient can afford to do so it is best that he return to routine work very gradually; but if he is to follow up his occupation he must be advised to reture at an early hour and rest after his chief meal for at least half an hour. Hydrotherapeutics in the form of mild douches or warm baths, in the summer season sea baths, are very beneficial.

Medicinally the most important part is the HCl and pepsin:

Acid. hydrochlor. dilute.,			
Pepsini puri	āā	5	10
Aquæ		50	100

S.—One teaspoonful in a glass of water, to be taken before and during the meal.

It may also be given in the form of acidol-pepsin tablets (No. 1 or 2, weaker or stronger), one dissolved in a tumbler of water thrice daily with meals. We are fully aware of the fact that HCl and pepsin do not exercise their beneficial effect by replacing the missing secretions, because they cannot be given in quantities large enough to bring about such an action without having a local and generally poisonous influence, and the secretions cannot be made to return in true achylia. The fact, however, that we clinically see improvement by HCl and pepsin must depend on the improved motility brought about by the above-named drugs. Because of the acid introduced into the stomach the pylorus remains closed for a longer time, the closure and opening of the pylorus depending on the Hirsch-Nehring-Pawlow-Cannon reflex occurs more regularly. Acid even in small

quantities excites peristaltic action, thereby mechanically influencing digestion.

When patients complain of loss of appetite it is still customary for some empirically to prescribe the so-called stomachics and amara (tet. mucis nam; extr. fluid. condurang.; mixtur. cuichon. comp.). As to the usefulness of these amara extreme views exist. From the stand-point of the physiological experiments of Carlson[33] and others the stomachics are not only beneficial but they are injurious, inasmuch as they diminish secretions. Many clinicians of great experience (Ewald, Boas), however, still claim favorable results. The ideal stand-point in exciting the appetite is taken by Wm. Sternburg, who states that the proper preparation and variety of food are the best means to that end.

In the gastric type of achylia gastrica, unlike the pure neuropathic type, saline mineral waters either at the spas or at home should be employed once a year for four weeks in the quantity of 250 c.c. taken hot in the mornings one hour before breakfast and one or two hours before supper. These waters do not exercise any curative influence on the achylia gastrica, but they bring about considerable improvement. That the waters taken at the spas have a better effect than when taken at home is due to the proper diet, pleasant surroundings, regular mode of life, and well-carried-out physicotherapeutics by trained men. It should be borne in mind that these patients have a tendency to be hypochondriac and proper psychical influence is most important.

When there is a marked tendency to constipation a course of olive-oil enemata lasting from two weeks to a month should be employed, and repeated in the course of intervals as the case may necessitate.

To the third group of cases belong those in which diarrhea is the main symptom. In a number of cases the discovery that the diarrhea is due to achylia gastrica gives us an encouraging hint that the diarrhea will be favorably influenced by the proper treatment. The treatment, however, must be individualized. Patients who have not the symptoms and signs of enteritis are benefited readily by the removal of the milk, by interdicting meat for a few days, and then gradually returning to well-done and finely chopped meat, not exceeding 200 to 250 grams a day. Raw fruits and coarse vegetables (beans, cabbage, lentils, etc.) must be forbidden. The diet consists of eggs, water cocoa, fine cereals (rice and barley in particular), with butter, toasted white bread, macaroni, fish, and cream cheese, and three-day old kumyss. Of the drinks red wines are beneficial. Medicinally, HCl and pepsin in the formula given above with and after meals and calcium citrate or calcium phosphate

[33] Jour. Am. Med. Assn., January 2, 1915; Jour. Phar. and Exp. Therap., November, 1914.

(Boas) in teaspoonful doses in a tumbler of water before meals are beneficial.

In more obstinate cases of diarrhea, and especially when the symptoms point toward enterocolitis, the diet should be restricted to strained barley soups, water cocoa, tea, rice, or sago soups cooked in water to which cinnamon is added for the taste, and almond milk. Almond milk is prepared as follows: Forty sweet almonds and two bitter almonds are placed in boiling water for a few minutes; then the almonds are peeled and ground. Add half a pint warm water, stirring constantly, and pass through a cloth. It should be allowed to stand on ice for two hours before drinking, and should be freshly prepared every day. One hundred grams of red wine are allowed in the course of the day. Such a diet is to be continued for three or four days, during which time the patient should stay in bed with hot poultices or a Prissnitz compress applied to the abdomen. Medicinally we start with 20 grams of castor oil, followed by tannigen 0.2 to 0.3 or tannalbin 0.5 two or three times daily. If there is still intestinal irritation saline enemata (2 teaspoonfuls to a quart of water) or an infusion of chamomile tea (1 to 2 teaspoonfuls to the quart) will prove beneficial. The return to a more substantial diet should be gradual. For at least one month the following diet list will prove efficacious:

Breakfast: One or two soft-boiled eggs, 4 slices toast or zwieback with butter, 250 grams water cocoa to which one or two yolks of eggs are added.

At 10 A.M.: One cup bouillon

At noon: Barley or rice soup; spring chicken or lean fish. Vegetables: 2 tablespoonfuls finely mashed potatoes or spinach or carrots in purée form. Should even these vegetables prove irritating the quantity should be diminished or removed. On the other hand if the patient stands it well we increase the quantity of vegetables. Farina pudding and 60 grams red wine.

At 4 P.M.: 250 grams almond milk or water cocoa with zwieback.

At 7 P.M.: One or two eggs; cereals with butter or barley soup. Oatmeal and barley should be strained. Toast and butter. Water cocoa with yolk of one egg. HCl and pepsin in the formula given above are beneficial, while stringents will probably not be necessary. Should, however, the enteric symptoms persist it is evident that we are confronted with an infectious enterocolitis either brought about, as claimed by Ad. Schmidt, by increase in the existing colon bacilli, or by the colon bacilli changing into virulent organisms, or the existing pathogenic organisms because of the favorable soil and the lowered resistance of the patient gain the upper hand. In this state mild astringents and intestinal antiseptics are necessary. The efficacy of astringents like bismuth subnitrate (0.5 to 1), or dermatol (0.5), tannigen (0.3), tannalbin (0.5), three times daily, is well established. The usefulness of intestinal antiseptics was rightfully disputed by

pharmacological experimentation and clinical results. It was shown that small doses have absolutely no effect while doses large enough to be effective are poisonous, and hence the large group like salol, resorcin, ichthyol, menthol, etc., have been discarded. Recent experiences in the present war with the infectious enterocolitis cases have brought forward the mode of administering large doses of intestinal antiseptics, bringing about a curative effect without injurious results. It was found that when drugs like kaolin (bolus alba, or fuller's earth)[34] or animal charcoal are given half an hour before the meal and the intestinal antiseptic half an hour after the meal not only is an absorptive effect on the bacteria and toxins achieved but the slow and minute absorption of the antiseptic into the blood is prevented by the charcoal or kaolin. In other words the antiseptic has its local effect and the rest is eliminated through the bowels with the absorbent substances.

The antiseptic chosen was thymol in doses as large as 0.5 to 1 three times daily half an hour after meals. Of course, other antiseptics, especially β-naphthol or resorcin, may be employed in the same manner. Caution as to the use of large doses of thymol is important. It should be begun with 0.3 to 0.5, and only when such doses are not effective may it be increased. Absolute constipation should be prevented by an occasional dose of castor oil, and the antiseptic should be discontinued as soon as the patient improves, because the prolonged use of thymol has a deleterious effect on the intestinal ferments. For cases in which the symptoms point toward a pancreatic disfunction (achylia pancreatica) we should, with Wahlgemut, restrict carbohydrates for a time; otherwise the diet list is the same as the one outlined above for achylic diarrhea. Medicinally, pancreon 0.5 three times daily after meals should be employed.

Rehfuss[35] has obtained results with parathyroid, one-tenth of a grain t. i. d., given for three-day intervals.

INDICATIONS FOR BLOOD TRANSFUSION.

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To simplify the discussion and condense the indications, I shall divide the conditions in which transfusion is necessary into classes and take up each class separately.

First class: Acute traumatic hemorrhage, both internal and external. This, of course, includes secondary hemorrhage.

[34] Hess: Jour. Am. Med. Assn., January 8, 1916.
[35] Am. Jour. Med. Sc., July, 1915, p. 72.

Second class: Hemorrhagic obstetrical complications.
Third class: Shock.
Fourth class: Hemorrhage from the viscera.
Fifth class: Anemia in non-malignant conditions.
Sixth class: Anemia in malignant conditions.
Seventh class: Anemia in tuberculosis.
Eighth class: Anemia in infectious diseases.
Ninth class: Blood dyscrasia.
Tenth class: Hemorrhage of the newborn.
Eleventh class: Poisoning.
Twelfth class: Delayed coagulation time.

1. Acute traumatic hemorrhage, both internal and external. This, of course, includes secondary hemorrhage. In just what degree of anemia in traumatic hemorrhage is transfusion necessary? This will have to be determined somewhat by the associated clinical symptoms, such as shock, etc. It may be said that with a blood count of 1,000,000 red blood cells and hemoglobin of 20 per cent. or below there is an absolute indication for transfusion, but when the count is 1,500,000 red blood cells and the hemoglobin above 25 per cent. it may or may not be employed, depending upon the associated symptoms. The above holds good for secondary as well as primary hemorrhage. It is, of course, assumed that the bleeding-point is controlled or can be controlled, as in hemorrhage from ruptured liver or spleen.

2. Hemorrhagic obstetrical complications. Postpartum hemorrhage, whether it is due to delayed coagulation time or not, has been one of the main indications since the earliest times of transfusion. In just what degree of hemorrhage it is necessary is questionable, and just the amount of blood required is difficult to determine. In the first place the rule as given above, of 1,00,000 or below, is an absolute indication, and 1,500,000 as a questionable indication holds good here. Hemorrhage in placenta previa or premature detachment may or may not require transfusion, depending upon the rapidity of the obstetrician, meaning of course, the loss of blood and associated shock. Transfusion is absolutely indicated if the count is below 1,000,000 or when there is associated shock, pallor, air hunger, etc. It often makes it possible to operate upon cases in which otherwise they would have died from cerebral anemia. It is absolutely indicated in cases of this type with greatly increased coagulation time.

3. Shock. In surgical shock *per se* without hemorrhage it is not as valuable as salt solution and adrenalin, but in shock associated with severe hemorrhage it is of decided value. Just what degree of shock in hemorrhage indicates transfusion must be determined in each case.

4. Hemorrhage from the viscera. In anemia from gastric hemorrhage, if hemorrhage producing the anemia was due to ruptured

varicose veins—a complication of cirrhosis of the liver—transfusion is contra-indicated, as it will only increase the hemorrhage by raising the blood-pressure; but if the anemia is a complication of an ulcer or postoperative bleeding from gastro-enterostomy, transfusion should be performed and immediately followed by abdominal section to control the bleeding-point. Of course, it has been assumed that the hemorrhage has been of sufficient severity as to cause a grave anemia. If the hemorrhage is from the intestines, as in typhoid fever or tuberculous ulcer, it may or may not be of decided value; but here the transfusion should be in small amounts, and frequently repeated so as not to increase the blood-pressure and thereby start the bleeding.

5. Anemia in non-malignant conditions. In non-malignant conditions or tumors in which on account of frequent small hemorrhages the patient is considered a bad operative risk he may be made a good operative risk by transfusion. This will, of course, allow of wide interpretation. Examples of conditions such as fibroid tumors, papilloma of the bladder, hemorrhoids, etc. In renal hemorrhage, whether of essential or other type providing the anemia is sufficiently severe, it is indicated as a preparatory treatment preliminary to operation.

6. Anemia in malignant conditions. In this condition at one time it seemed from experimental studies that there was going to be a large and brilliant field. This, however, under the clinical test has proved to be erroneous. It has practically no effect upon the course of the malignancy, and is only indicated as a means of overcoming the anemia as a preparatory stage for other treatments.

7. Anemia in tuberculosis. Here as in malignancy it has been frequently used to control the tuberculosis instead of being used, as it should be, as a means to overcome the anemia. In pulmonary hemorrhage it is usually not indicated, but in very severe types of anemia from this case transfusion may be used in small repeated transfusion, being careful not to increase the blood-pressure and start up the bleeding. As a preliminary procedure to operation upon any tuberculous subject who has been a severe anemic it is, of course, indicated. In miliary tuberculosis it has no effect upon the disease.

8. Infectious diseases. In infectious diseases, such as typhoid fever, scarlet fever, etc., it is of no value. In cholera it has been said to be of decided value on account of the rapid loss of fluid and the subsequent anemia. I have had no personal experience with it. In acute sepsis no permanent results have been noted by careful observers. In pellagra various results have been recorded, some claiming wonderful results, others condemning it. As I have had no personal experience, I must depend upon the published results. It could at least be said that there are no deleterious results, and there has been some temporary improvement. In infectious diseases then it can be said that there is no specific effect upon the

infection by the transfusion, but if any anemia is present it is temporarily improved.

9. Blood dyscrasiæ. In hemophilia it will have the effect of correcting the anemia, and if given in sufficient amounts will usually cause the coagulation time to approximate the normal. The effect upon the coagulation time, however, is usually only of value for a short time, and only in exceptional cases does it have a permanent effect in overcoming the delayed coagulation time. In pernicious anemia the results have been very discouraging, and at times very satisfactory. As this disease tends to have remissions, it may be that if transfusions were performed on the upward curve the results would have been more permanent and satisfactory. The least that can be said is that a limited number have been cured, many have been benefited, and there ought not to have been any injured. The transfusion should be repeated several times at approximately weekly intervals. It is of decided advantage in preparing these patients for removal of the spleen. In leukemia several cures have been reported by repeated transfusions, as has also several unfortunate calamities. I have no personal experience, so must depend upon the reports of others. It is one of the blood dyscrasiæ in which I do not think transfusion is indicated. In splenic anemia and Banti's disease it is only of value as a method for correcting the anemia or as a preparatory measure for splenectomy.

10. Hemorrhage of the newborn, melena, etc. In most of these cases, serum or defibrinated blood is all that is necessary, but in very severe anemia it is indicated, as it is the only treatment that will benefit these cases; but the pathology of these cases must be remembered, that is, frequently there are large hemorrhages into the lungs, liver, etc., before there are any external signs of bleeding. The pathology, of course, accounts for why a certain percentage of these cases die after transfusion. In any case, care should be exercised in giving more than a moderate amount, and this under low pressure to prevent dilatation of the right heart.

11. Poisoning. In gas-poisoning, illuminating and otherwise, it is of limited value and should only be used after very severe vena section, as it is the toxemia and not the anemia that is the point to be corrected. In poisoning from coal-tar derivatives with the chocolate-colored blood it will be found that a severe vena section with salt solution will usually give results equal to transfusion. In the metallic poisoning I have not seen any results. In acute bichloride-poisoning, however, I have been tempted to perform large vena sections and transfuse large amounts, but have not seen a suitable case.

12. Delayed coagulation time. In delayed coagulation time from whatever cause it is frequently on account of the severe anemia desirable to overcome the deficient coagulation time rapidly, or it may be that one or more of the constituents of the blood, such as

fibrinogen are absent and blood serums or blood placquelets, will not give the desired results. In this condition it has the double effect of correcting the anemia and shortening the coagulation time.

The indications for transfusions may then be practically summed up in the following manner: It may be used in any condition to correct a very severe anemia or it may be the only method of rapidly controlling a lengthened coagulation time.

DIABETES INSIPIDUS.

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Our knowledge of diabetes insipidus at the present time is well examplified by the fact that of those who have given careful consideration to this pathological manifestation, some call it a "disease" while other authorities prefer to designate diabetes insipidus as a "disease syndrome." Diabetes insipidus is of comparatively rare occurrence, being about 14 in 100,000 patients. One therefore approaches each new case with interest, and with the hope of finding a clue to its etiology and proper treatment.

In a very interesting study, Fitz[1] calls attention to the fact that diabetes insipidus was recognized in 1682 by Thomas Willis, and well described by Johann Peter Frank in 1794, and it is remarkable that so little information has been gathered since that time. This, however, may be due to the fact that diabetes insipidus does not have a definite anatomical basis, or if it does, it certainly has escaped detection. In more recent times the problem of diabetes insipidus is being approached by the avenue of functional pathology, and results seem more promising.

Diabetes insipidus may be defined as a disease state characterized y an excessive polydipsia and polyuria.

According to various observers it has been known to occur when there was an hereditary tendency to the disease; it has been known to occur after fevers, after physical injury to the brain and cord, after psychic trauma, after luetic disease of the nervous system (particularly basilar meningitis), after tumor of the brain, and after tumor or irritation or injury to the hypophysis, such injury being accidental or following surgical interference, and also after injury to the temporal region of the brain, and particulrly after injury in the region of the floor of the fourth ventricle. Diabetes insipidus has been known to occur in cases of carcinoma of the liver and of the adrenals (by metastasis?), and in disease of the pancreas.

[1] Arch. Int. Med., 1914, xiv, 706.

It will be of interest to cite the tendency of modern opinion held by those who have studied this condition. Allen[2] says: "In general there seems to be ground for believing that diabetes insipidus belongs among the disorders of internal secretion. The facts are not yet sufficient to warrant a conclusion or hypothesis."

Falta[3] states: "We must leave the genesis of the disease open." Fitz holds: "On the whole it appears that diabetes insipidus is usually of the symptomatic type, though it may be of the idiopathic. The exact cause of the polydipsia and polyuria is undetermined. Certain observers believe that the concentrative powers of the kidneys are at fault, others that the polyuria results from an abnormal thirst." Barker[4] likewise holds the view that there are two forms of this disease: the idiopathic diabetes insipidus, due to a functional disturbance of the kidney, which makes them incapable of secreting a concentrated urine, and the symptomatic diabetes insipidus, in which there is no functional insufficiency of the kidneys. The polyuria is secondary to a primary polydipsia, this latter type being of neurogenic origin or due to some disturbance of internal secretion.

The case reported by Fitz showed that the kidneys were capable of performing a normal amount of work, but there was a particular sensitiveness to salt. The ingestion of 25 grams of sodium chloride brought on a marked diuresis, "vascular hyposthenuria."

The case to be reported here will be presented from the standpoint of functional capacity of the kidney, whether the kidneys were hypersensitive to urea, chlorides, and glucose, and to record those other observations which time and circumstance permitted. Excepting for one day in the hospital the patient was an ambulatory case, and it required much tact to procure the observations which I was permitted to make, as he had already seen many physicians, and did not care to lend himself to extended observations.

Case History.—W. C. B., male, aged forty-eight years; family history is good; previous health good. No history of venereal disease, accident, or trauma. In August, 1912, had an attack which his physicians designated congestion of kidneys; recovery was good. Eighteen months ago, independent of everything else, he developed polydipsia and polyuria, but no polyphagia. Fourteen months ago had an attack of "grip," followed by exsiccation and exfoliation of skin and mucous membranes. Since the onset of polyuria he has been passing from 6 to 11 quarts of urine daily. Five years ago he weighed 175 pounds, six months ago 190 pounds, and now weighs 195 pounds; so that, irrespective of the polyuria, his body weight has increased and his nutrition is apparently unaffected.

He follows his occupation, cattle rancher, which entails much

[2] Glycosuria and Diabetes, Harvard Univ. Press, 1913, p. 523.
[3] The Ductless Glandular Diseases, Blakiston, 1915, p. 323.
[4] Monographic Medicine, iv, 815.

physical exertion, and frequently hardships. His diet is that of many American workmen, high in protein. He eats eggs, fruit, and coffee for breakfast; meat, vegetables, dessert, and coffee for luncheon; soup, meat, vegetables, coffee, and dessert for dinner. His physical comfort varies with his ability to get water.

In the foothills of the Rocky Mountains, for a distance of forty miles from the Main Divide, he nearly always manages to get a supply of good water while crossing streams, at least once in three hours. But when he gets in the low country, where the soil and the water are both rich in alkali, he suffers much inconvenience. The alkali water and the sulphur waters are undesirable for drinking, and with him, as with the other men, it frequently causes an irritability of the bladder.

Physical Examination. Height, 5 feet 6 inches; weight, 195 pounds; general type, robust. Skeleton and features normal. Head and neck negative. Vision normal. Radiograph shows a normal sella turcica. Chest: lungs negative, heart negative. Blood-pressure: maximum, 156; minimum, 97; pulse, 84. Abdomen negative. Extremities negative. Reflexes normal. Glands negative. Gastro-intestinal history negative. Nervous system negative. Circulatory history negative. Blood count normal. Wassermann negative. Urine shows trace of albumin; no casts.

Water Excretion. The patient did not lend himself to the water test, as his thirst seemed unsatiable. He would not or could not control the thirst sufficiently to permit a starting-point for the test, aside from the difficulty he would have had in taking an amount of water greater than he was already drinking.

His average excretion was 500 c.c. to 600 c.c. per hour.

Polydipsia. This was the patient's chief complaint, his inordinate desire for water, and it was, as he said, not because of his need for the water, which when it reached his stomach made him feel oppressed and uncomfortable, but that he craved the water to allay the horrible "leathery" taste in the roof of his mouth, pharynx, and back of his tongue. Abstinence from drinking made him feel that his parched tongue would stick to the roof of his mouth and the back of his throat." Even copious rinsing of the mouth did not relieve him. This parageusia may indicate an alteration in function or structure of the glossopharyngeal nerve or central involvement at the medulla. Blocking of that nerve would have been an important experiment in this case had it been possible.

Hyposthenuria. For a period of one month, during which the patient kept careful account of his daily urinary output, the maximum was 12,450 c.c. and the minimum 11,000 c.c., the average secretion being 11,670 c.c. per day. During a period of three days, on a constant diet, the patient received successively 20 grams of urea, 10 grams of salt, and 100 grams of glucose. After the urea he excreted 13,396 c.c., after the salt 13,110 c.c., and after the glucose

12,930 c.c.; so that in response to the increased presence of these substances in the blood we find there was greater demand for water and a larger urinary excretion.

Conversely, when the patient was placed on a Mosenthal salt-free diet the total excretion within the following twenty-four hours decreased promptly from 12,930 c.c. to 10,500 c.c., a fall of 2430 c.c. in twenty-four hours. How the kidneys responded to each one of the substances separately will be referred to later.

Specific Gravity. This varied between 1000 and 1003; the latter concentration was attained on the day the urea was taken.

Urea Excretion. In the twenty-four hours following the ingestion of urea the specific gravity rose from 1001 to 1003, and the entire 20 grams of urea were eliminated. This shows a definite ability on the part of the kidney to concentrate urine. The urinary output was 13,396 c.c., evidencing a greater than average desire for water and proportionate elimination. There was no hypersensitiveness to urea.

Salt Excretion. After 10 grams of salt given on the day following the urea the total volume of urine was slightly diminished; the specific gravity was 1001. The salt was eliminated promptly as the urea was, 9.4 grams in the twenty-four hours. There was no hypersensitiveness to salt.

Glucose. Four and a half hours after supper 100 grams of glucose were taken. This was followed by a diuresis of 2640 c.c., which kept him awake during the next four hours. A portion of this four-hour specimen of urine reacted positive to Benedict's, Almen-Nylander's bismuth test, and produced fermentation. Quantitatively, the amount was too small for estimation.

That glucose does not ordinarily produce a diuresis was shown by Taylor and Hulton,[5] who administered from 200 to 500 grams of glucose in twenty normals and rarely found a diuresis.

Hydrogen Ion Concentration of the Urine. As tested on several occasions I found to methyl orange the reaction was alkaline, to methyl red it was alkaline, to phenolphthalein acid and to Kahlbaum's neutral litmus it was slightly acid.

The hydrogen ion concentration of the urine may therefore be recorded as being 10 to 9, or about normal.

Salt-free Diet. Placing the patient on a Mosenthal salt-free diet resulted in a prompt decrease of 2400 c.c. urine during the following day. The salt elimination was moderately diminished and urea was decreased by exactly half of the previous day.

Phenolsulphonephthalein Output. Dye appeared in ten minutes. At the end of the first hour there was 600 c.c. of urine, specific gravity 1004, and dye elimination 16 per cent. Total phenolsulphonephthalein elimination, 69 per cent.

[5] Taylor and Hulton, Jour. Biol. Chem., 1916, xxv, 173.

Lumbar Puncture. Upon entering the spinal canal the fluid came through the needle in a steady stream, which had not diminished when 25 c.c. was removed. I thought it inadvisable to remove more, and stopped. There was no increased pressure behind the flow, and I looked upon this as being one phase of the general flux of fluids in the body of this patient. This may prove to be an important observation that in some cases at least the greater liquid exchange is not limited to the kidney.

On the day preceding lumbar puncture the urinary output was 12,000 c.c.; on the following day, the patient having been kept in bed, it was 7950 c.c.; on the next day the patient was up and about, and it was again 12,000 c.c. Lumbar puncture had no more than a transitory if any influence upon the polyuria. No cells were to be found in the fluid. The globulin test was negative, sugar reaction slight, and the Wassermann in quantities of 0.2, 0.4, and 0.8 c.c. was negative. I now believe that we should have used much larger amounts of the spinal fluid as well as the blood for Wassermann tests on account of the high dilution of the body fluids.

Saliva. Upon examination of the mouth it was readily seen there was a copious salivary flow, as the saliva trickled down the inner cheek from the mouth of Stenson's duct in a continuous stream. The salivary secretion from the sublingual gland was likewise profuse. To Kahlbaum's neutral litmus the reaction was acid. We may account for the sialorrhea in several ways: (1) as with urinary flow and the spinal fluid, the liquid exchange or flow through organs which normally secrete a fluid is abnormally large; (2) that the sialorrhea is physiological and occurs in response to the parageusia through stimulation of the parotid gland; (3) that the sialorrhea is pathological and is the product of an abnormal stimulation or disease of the nerves governing the function of the gland, glossopharyngeal, or its centre in the medulla. The salivary glands are sensitive to stimulation, $\frac{1}{5}$ grain of pilocarpin markedly increased the already large flow of saliva.

Drugs. Without going into details of the pharmacological action of these drugs I merely note the effect of the following drugs:

Atropin, grain $\frac{1}{50}$ t. i. d. for four days, caused no change in amount nor concentration of urine.

Sodium nitrate, gr. iij, q. i. d., no effect.

Potassium bromide, gr. 10 q. i. d., no effect.

Pilocarpin, gr. $\frac{1}{5}$ produces a marked diuresis lasting two hours, during which time there is eliminated 500 to 1000 c.c., more urine than is normal for him. After two hours there is a decrease, also lasting two to three hours, after which time the normal rate of flow is resumed.

SUMMARY. A case of diabetes insipidus with kidneys capable of eliminating a normal amount of solids in the twenty-four hours. In response to ingestion of added amounts of salt and urea the

kidneys show ability to eliminate these substances promptly and to concentrate urine. In response to the ingestion of 100 grams of glucose the urine showed a trace of sugar and a diuresis followed. Phenosulphonephthalein elimination was normal. There were evidences in this case suggesting that the abnormally large liquid exchange was not limited to the kidneys, but that the spinal fluid and saliva were likewise secreted in abnormally large amounts.

It was demonstrated that although the kidneys and salivary glands were already performing an inordinate amount of work, as far as excretion of water is concerned they were not functioning to their maximum capacity.

Pilocarpin produced a sialorrhea and diuresis after each dose on several days. Circumstances did not permit any attempt at determining the part played by the internal secretions in this case, nor was it possible to make any observations toward determining the part played by the glossopharyngeal nerve in the polydipsia.

THE METASTASIS OF TUMORS: A STUDY OF 298 CASES OF MALIGNANT GROWTH EXHIBITED AMONG 5155 AUTOPSIES AT BELLEVUE HOSPITAL.

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There are reasons for believing that as a result of accident or other fortuitous circumstance, or even in the ordinary course of events, certain fixed cells may become liberated into the circulation, *e. g.*, placental cells may be freed and transported to the liver, and liver cells may be released and carried to the lungs. In either event proliferation of the transplanted cell is obstructed not only by equilibrium of function in the cell itself, but by the innate antagonism of the tissue in which it finds lodgment. There are equally acceptable reasons for believing that the cells of certain tumors are more or less constantly discharged into the blood stream and destroyed. Seldom is this destructive property placed in abeyance, as is evidenced by the rarity of universally disseminated metastases in human tumors and by the low proportion of successful inoculations following injection into the blood stream of emulsions of the transplantable tumors of lower animals. The lymph stream, on the contrary, seems to be devoid of inimical properties, and the tumor cell, particularly the epithelial variety, not only

obtains hospitable lodgment in the lymph spaces, but finds conditions favorable for its growth.

The quality of anaplasia and the capacity to infiltrate and metastasize combine to form the most dependable of the several criteria by which the malignancy of a tumor is judged. There are instances, however, in which misplaced groups of cells are not only suspiciously arranged, but exhibit distinct anaplastic peculiarities together with a noticeable disposition to remain circumscribed and at rest. For example, there is a carcinomatoid formation occasionally to be seen in the lower end of the small intestine that possesses marked anaplastic features, and, from the general appearance of a given microscopic field the pathologist would be entirely justified in pronouncing the growth malignant, yet local expansion seems seldom to trespass beyond bounds, and metastasis is practically unknown. A closely related variety of growth is not infrequently encountered in the appendix and is likewise of little significance.[1] The same, in part, is true of the pigmented cutaneous mole, the histological structure of which bears a striking resemblance to that of a malignant tumor. The fact that the proliferative capacity of the skin mole is sometimes exalted into malignant growth does not vitiate the contention that anaplastic cells may remain indefinitely at rest, since the tendency of the cutaneous mole is in the direction of quiescence, and malignant transformation occurs relatively rarely, and only in circumstances of irritation or injury.

On the other hand, certain cells possessing negligible histological indications of anaplasia are capable of diverting a considerable proportion of their energy to the process of growth, not only locally, but in situations removed from their place of nativity. Thus, chondromata may metastasize, and there is at least one case in the literature, sponsored by no less an authority than Orth,[2] of a metastasizing myofibroma of the uterus.

Interesting and important as these growths may be, both from an academic and practical stand-point, they are of negligible significance when compared with that larger category of neoplasms whose cells are frankly anaplastic and whose capacity to metastasize is exercised with such appalling freedom, namely, the carcinomata, sarcomata, and cognate growths. It is with this group that this paper deals, and I shall correlate the results of an analysis of 298 malignant tumors encountered among over 5000 autopsies at Bellevue Hospital with special reference to their metastases, the distribution of which often assumes great practical significance.

Incidence. Among 5155 autopsies at Bellevue Hospital in the past ten years there were 298 malignant tumors. Thus, 5.78 per cent. of all patients dying in Bellevue Hospital and coming to autopsy are subjects of malignancy. Of the 298 tumors, 264, or

[1] Rolleston and Jones: Lancet, June 2, 1906, p. 1527.
[2] Krische: Inaug. Dissert., Göttingen, 1889.

89 per cent., were of the epithelial or mesothelial variety, and 34, or 11 per cent., were sarcomata or endotheliomata. Therefore the proportion of epithelial to connective-tissue tumors in the series, as a whole, is 8 to 1.

Of the 298 tumors, 220, or 74 per cent., had gone to the stage of metastasis; in 19 instances, or 7 per cent., there was direct invasion of neighboring tissues without attendant metastases in remote parts, and in 59 cases, or 19 per cent., the growths remained localized as follows: Epithelioma of the urinary bladder 7, of the tongue 4, of the cheek and bronchus 1 each, of the esophagus 7; carcinoma of the stomach 10, of the sigmoid 6, of the cecum 5, of the uterus 3, of the rectum, pancreas, and liver 2 each, of the bile ducts and breast 1 each; sarcoma of the lung and osteosarcoma of the vertebræ 1 each, hypernephroma of the kidney 3, and of the adrenal 1.

The primary growths were distributed thus: epithelioma of the esophagus 23, of the urinary bladder 12, of the tongue 5, of the branchial clefts, bronchi, skin, and larynx 2 each, of the pharynx and penis 1 each; carcinoma of the stomach 84, of the gall-bladder 16, of the prostate 12, of the bile ducts 6, of the cecum 10, of the duodenum 3, of the pancreas 10, of the uterus 11, of a salivary gland and the jejunum 1 each, of unknown origin 2; hypernephroma of kidney 12, of adrenals 3; lymphosarcoma of the retroperitoneal nodes 4, of the anterior mediastinal nodes 3, of the posterior mediastinal nodes 2, of the cervical nodes 2, of the gastro-intestinal lymphoid structures 2, of general distribution 1; sarcoma of the breast 1, of the retroperitoneal nodes 2, of the periosteum 2, of the humerus, cervical nodes, sole of foot, thigh, mesenteric nodes, lung, and kidney 1 each; osteosarcoma of right leg, left leg, vertebræ 1 each; multiple myelogenous sarcoma 2, melanoma 1.

Of the 298 tumors the lymph nodes were metastasized 131 times, or in 44 per cent.; the liver 102, or in 34 per cent.; the pleura and lungs 73, or in 25 per cent.; the bones in 35, or 17 per cent.; the vertebræ, ribs, calvarium, sternum, femur, humerus, and pelvis being involved in the order named; the adrenals were metastasized 23 times, or in 8 per cent.; the kidney 17 times, or in 5.7 per cent.; the spleen 16 times, or in 5.3 per cent.; there was neoplasmic invasion of large veins in 13 cases, or in 4.7 per cent.; the pancreas was metastasized 13 times, or in 4.7 per cent.; the heart muscle 9 and the skeletal muscles 3 times, or in 4 per cent.; the ovary, mesentery, pericardium, and dura mater 7 times each, or in 2 per cent.; the small intestine, stomach, and scalp 3 times each, and the testicle and esophagus once each.

The figures just quoted show that as far as metastasis is concerned the organs of the body are divisible into a group the members of which are frequently the seat of metastasis, but in which primary growths are rare; a group composed of organs which are commonly the seat of primary growths, but which are rarely

metastasized; and a group the members of which are neither the seat of frequent tumor growth nor of metastases.

THE ADRENALS. The adrenals were the seat of metastases in 23 instances, or in 8 per cent. The secondary growths were derived from cancer of the stomach 5 times, the breast 4 times, the gall-bladder and liver 2 each, the duodenum and splenic flexure 1 each, from hypernephroma of the kidney once, and from sarcomata 6 times. Both adrenals were extensively metastasized 12 times (52 per cent.), and of this number the glands were completely destroyed in 8, or in 35 per cent. In addition to destruction of the adrenal bodies by secondary growths, there were 3 cases of bilateral adrenal hypernephromatosis attended by complete transformation of the glands into tumor tissue. Thus, both adrenals were completely or almost completely destroyed in 15 cases, or in 65 per cent. of the total number of neoplasmic lesions found in them, and in not one of the number was pigmentation of the skin or mucous membranes observed at autopsy, nor were these or other signs of Addison's disease detected during life.

The suprarenal capsule represents, developmentally, two sets of organs which, in higher forms, are fused, the cortex originating in the mesoderm and the medulla in the neuro-ectoderm. It is not astonishing, therefore, that pathologists have been able to differentiate in man two genetically and clinically separable varieties of neoplasm arising in the adrenal body, one of cortical and the other of medullary origin. The adrenal hypernephroma, which is composed of cells of cortical origin, is attended, in the young at all events, by excessive bodily growth and precocious development of the genitals and the secondary sexual characteristics.[3] These facts harmonize with the generally accepted view that the adrenal cortex is of companion origin with the testicle and ovary. On the other hand, there is a familiar group of tumors of the kidney the individual members of which are composed of cells morphologically resembling, if not in distinguishable from, the cells of the suprarenal cortex—the so-called renal hypernephromata. These tumors are composed of cells which, according to one view, are derived from nests of adrenal mesothelium aberrant in the renal cortex or otherwise misplaced, as in the liver, according to another view, they spring from adenomata of the convoluted tubules of the kidney.[4]

The suprarenal tumor of medullary origin is the neuroblastoma, and it arises from residual foci of embryonal nerve cells. Just as the development of the adrenal cortex is in striking contrast to that of the medulla, so is the neuroblastoma noticeably dissimilar from the hypernephroma. Thus, it has been shown that the adrenal medulla is an integral part of the chromaffin system and develops

[3] Bulloch and Sequeira: Tr. Path. Soc., London, 1905, lvi, 189.
[4] Alexander Fraser: Surg., Gynec. and Obst., June, 1916, p. 645.

in connection with the sympathetic. At a certain stage in its evolution there appear collections of so-called formative cells from which arises all that is cellular in the sympathetic system, including ganglion cells and the chromaffin constituents of the adrenal as well as of other localities. Termination of embryonal life does not necessarily denote completion of evolution in the adrenal medulla, but, on the contrary, the medulla is almost exclusively a product of postembryonal development, and up to, or even slightly beyond puberty, it contains collections of formative cells, or neuroblasts, constituting a source of potential tumor growth. Doubtless future investigation will show that aberrant formative nerve cells are of frequent occurrence elsewhere, that is to say, beyond the confines of the adrenal medulla, since isolated examples of neuroblastoma have been described in the cerebellum, at the root of the lung, in the soft tissues of the scapular region, and elsewhere.[5]

Thus far the neuroblastoma has been observed oftenest in children, in whom, it would appear, the growth is separable into two symptomatic groups, one attended by extensive metastases in the cranium and regional lymph nodes attended by secondary exophthalmus and ecchymosis of the lids, the other by rapidly increasing distension of the abdomen due to neoplasmic infiltration of the liver without ascites or jaundice.

Hypernephroma. Hypernephroma of the adrenal, as already indicated, occurring before the onset of puberty, brings about certain changes in bodily growth and in the development of the genitals and the secondary sexual characteristics. Developing after puberty, the lesion pursues the ordinary course of neoplasmic growth, and is marked by a palpable mass in the abdomen or even by visible enlargement corresponding to the location of the tumor, by irregular elevation of temperature due to absorption of the products of necrosis, and by pain. When the growth invades the pelvis of the kidney, as it not infrequently does, hematuria results, and may be constant or intermittent. In some cases the tumor grows slowly and remains localized, in which event operative removal may be followed by complete cure. In other instances the tumor grows with surprising rapidity, and not only attains enormous size, but infiltrates surrounding structures and gives rise to widespread metastases, particularly in the bones, lungs, and larger veins. In occasional cases signs of bone metastasis give the first indication of intra-abdominal growth, in other instances hemoptysis or hemorrhagic pleural effusion arising from intrathoracic metastases constitute the initial clinical disturbances.

In the Bellevue Hospital series of autopsies there were 15 cases of hypernephroma. Three arose in the adrenals, and all of them occurred in adults; 2 were bilateral. One was localized, and, of

[5] Douglas Symmers: Jour. Am. Med. Assn., 1913, lx, 337.

the other 2, one was accompanied by extensive metastases in the lungs, by a solitary metastasis in the scalp and liver, and by neoplasmic thrombosis of the inferior vena cava and both adrenal veins. In the remaining case the left adrenal measured 30 x 18 x 15 cm., and the right 15 x 8 cm., and there were numerous metastases in the pleura and lungs, in the retroperitoneal nodes, and a solitary metastasis in the heart.

Of the 12 cases of renal hypernephromata, the primary growth was in the left kidney in 7, and in the right in 5. The lower pole, contrary to the prevailing notion of the topographical origin of hypernephroma of the kidney, was the site of growth in 5 cases, the upper pole in 3, and in the other 4 cases the place was not recorded. Of the 15 cases metastases were present in the pleura and lungs in 9 (60 per cent.), and of these the peribronchial nodes were infiltrated in 4. The liver was extensively metastasized in 6 cases (40 per cent.), in 5 of which the pleura and lungs were also involved. Of the 15 cases the venous system was invaded seven times (46 per cent.), the inferior cava, renal, adrenal and iliac veins being chiefly concerned. Thus it appears that the hypernephroma exhibits little favoritism in the method of spreading its metastases, but embolizes the blood and lymph streams and infiltrates contiguous structures with scarcely discernible discrimination.

In 5 cases (33 per cent.) there were metastases to the bones, the vertebræ and ribs being oftenest affected.

The Veins. Neoplasmic invasion of the larger veins occurs occasionally, and is brought about primarily by direct extension and secondarily, by the lodgment of emboli. In the Bellevue Hospital series there was direct invasion of bloodvessels, with or without subsequent thrombosis, in 13 cases. Cancer of the gallbladder invaded the right renal vein once, in another case the right iliac vein was infiltrated, and in a third case there was neoplasmic thrombosis of the portal vein giving rise to blood-stained ascites. A case of medullary carcinoma of the stomach was attended by neoplasmic thrombosis of the splenic vein followed by numerous small metastases in the spleen due to retrograde embolism. In another case of gastric cancer there was neoplasmic thrombosis of the left iliac vein. In still another case neoplasmic thrombosis of the portal vein was associated with an enormous sarcoma of the pancreas. The remaining 7 cases (46 per cent.) of neoplasmic invasion of bloodvessels were directly traceable to renal or adrenal hypernephromata.

Ovaries. The ovary was metastasized in only 5 cases—4 times in primary cancer of the stomach and once in a cancer of the breast. The right ovary was alone involved in 3 cases, the left in 1, and in 1 case both ovaries were infiltrated.

There is a metastatic neoplasm of the ovary, however, which would appear to deserve rather more detailed consideration, namely, the

one described by Krukenberg[6] in 1896. This investigator, working in Marchand's laboratory, observed 6 examples of a malignant tumor which he believed to be of ovarian derivation and which is composed of a stroma richly infiltrated by large, mucus-bearing cells counterfeiting the shape of a signet ring. He was unable, however, to determine the origin of the cellular unit, and was consequently at a loss for a descriptive designation of the growth as a whole, but finally gave it the ponderous and rather equivocal title of "fibrosarcoma mucocellulare ovarii (carcinomatoides)." Since the appearance of Krukenberg's paper other observers have noted a growth in the stomach wall of identical histology, and have advanced the view that the tumor is primarily gastric and that the ovarian changes are metastatic.

The so-called Krukenberg tumor appears to be little known in this country. In fact, I know of but one case a description of which appears in the English language (Outerbridge[7]) and there is no acceptable portrayal of the subject in any of the English or American text-books with which I am familiar. Three cases have come to my notice in New York City in the past ten years—2 occurring in the surgical service of the New York Hospital and 1 at Bellevue Hospital. It was not practicable to investigate the New York Hospital cases beyond the field opened by surgical interference. Suffice it to say that in both cases the ovaries were regarded as primarily involved and were removed. The Bellevue Hospital case was made the subject of thorough postmortem investigation, and is as follows:

The patient, N. D., aged thirty-two years, married, was admitted in the twentieth week of pregnancy. For five months previous to admission she had been mentally dull and for some time had suffered severe attacks of vomiting. Two weeks before admission vomiting became incessant and was accompanied by epigastric pain. She had lost greatly in weight.

Autopsy. Throughout the parietal peritoneum were numerous flat, firm, whitish plaques from 1 to 2 mm. in diameter. The left ovary was sclerotic and cystic, but showed no naked-eye indications of infiltration. The right ovary measured 6 x 4 cm. and was nodular. The pyloric region of the stomach presented a firm, grayish mass which extended along the lesser curvature for a distance of several centimeters. The regional lymph nodes were infiltrated and there were a number of nodules embedded in the mesentery of the large intestine.

Microscopic examination of the right ovary, stomach, and peritoneal metastases showed the presence of infiltrating cells identical with those described by Krukenberg—that is to say, large cells with sickle-shaped nuclei peripherally placed, a relatively small

[6] Arch. f. Gynäk., 1896, p. 287.

[7] Am. Jour. Obst., 1911, lxiv.

amount of pinkish staining cytoplasm, and a larger amount of cytoplasm composed of granules staining reddish violet with weak aqueous thionin. According to unpublished work by M. E. Hall in the laboratories at Bellevue Hospital the characteristic cells of the Krukenberg tumor are derived from the parietal cells of the fundus glands in the mucosa of the stomach. From a study of Hall's preparations and the microscopic sections of the two tumors encountered by myself at the New York Hospital, I am strongly inclined to accept this view as the most satisfactory of the several that have been presented.

KIDNEYS. The kidney was metastasized seventeen times (7 per cent.). The metastases were derived from sarcomata eight times (47 per cent.), and from gastric, duodenal, and breast carcinomata seven times (43 per cent.), from an adrenal hypernephroma once, and from an hypernephroma of the opposite kidney once. Both kidneys were involved in 8 cases, the right was alone involved five times and the left four times.

SPLEEN. In 298 malignant tumors the splenic pulp was metastasized sixteen times, or in 5.3 per cent. Of the 16 cases, 14 were tumors of epithelial origin and the remaining 2 were sarcomata. The preponderance of epithelial tumors, however, is apparent rather than real, for the proportion of 7 to 1, which obtains for the series as a while, is likewise applicable to the metastases in the spleen.

Not only are splenic metastases of rare occurrence, but they are practically always small in both size and number, seldom growing beyond 1 cm. in diameter and rarely exceeding a half dozen. In but one of the Bellevue Hospital autopsies was an exception found, and in that case the spleen was riddled by small metastatic deposits following neoplasmic thrombosis of the splenic vein occurring in association with a medullary cancer of the stomach. Moreover, in every one of the 16 cases there were numerous metastases in other organs, notably the liver, lymph nodes, one or both adrenals, the bone marrow, peritoneum, omentum and mesentery.

In 7 cases the metastases in the spleen were derived from carcinomata of the stomach (43.7 per cent.), in 3 cases the primary growth was in the breast (19 per cent.), in 1 case there was a primary hypernephroma of the kidney, in 1 case a primary carcinoma of the liver, in 1 case the cecum was the point of origin and in 1 case the jejunum.

BONY SYSTEM. From the stand-point of metastasis the tumors of the osseous system are divisible into three groups. One includes those tumors which appear to have multiple points of origin within the osseous system itself, and which may or may not erode the cancellous bone and bring about infiltration of neighboring structures, but in which metastasis is practically unknown. This group includes the multiple myelomata,[8] the multiple primary giant and

[8] Vance: AM. JOUR. MED. SC., November, 1916, p. 693.

spindle cell growths described by Barry[9] and by Martland,[10] and the multiple primary intravascular hemangio-endotheliomata recently described by Symmers and Vance.[11]

The second group includes the spindle and giant-cell sarcomata, and other varieties of connective-tissue growth in which metastasis may occur in other parts of the bony system as well as in the soft tissues and viscera.

The third group embraces those tumors whose metastases display a distinct predilection for the osseous system, bringing about two widely remote series of changes—one characterized by osteosclerosis, as typefied by the growth of certain metastases of prostatic origin, and the other by destructive changes in the bones due to deposits from such tumors as cancer of the breast, thyroid, and stomach and the hypernephromata.

Bone Metastases. Bone metastases may be single or multiple, visible or palpable, or so successfully concealed that they may not be detected even at autopsy, or they may be suddenly revealed by spontaneous fracture of an extremity ensuing upon trivial cause, or by sudden or gradual development of symptoms referable to pressure upon the spinal cord following displacement of the vertebræ. In one of the Bellevue Hospital autopsies the patient complained during life of hoarseness and of excrutiating pain on swallowing. He suddenly developed paresis of both lower extremities, attended by disturbances in sensation and urinary symptoms. The knee-jerks were not obtainable. At autopsy there was a tumor in the upper portion of the esophagus lying directly under an intact mucous membrane. The bodies of the lowermost cervical vertebræ were infiltrated and displaced, producing pressure upon the cord. Microscopic examination of the growth in the esophagus revealed an adenocarcinoma derived from an aberrant salivary gland with structurally identical metastases in the spinal column.

In still another type of case the symptoms of bone metastasis are essentially those of pressure on the sensory nerve roots.[12]

Another and not uncommon variety of bone metastasis is solitary, and surgical removal of the secondary growth sometimes appears to be not only justifiable but imperative, particularly when the primary growth is accessible, as in cancer of the thyroid, the majority of whose metastases are single, grow slowly, and are often so situated as to invite removal, *e. g.*, in the lower jaw, humerus, femur, and sternum. Whether the thyroid itself should be removed is a question demanding the highest surgical judgment. Thus, in the case of a woman, aged forty-two years, who suffered a fracture of the humerus from a trivial cause, a quantity of softened and hemorrhagic tissue

[9] Quoted by Martland, loc. cit.
[10] Proc. New York Path. Soc., 1915, xv, 119.
[11] Am. Jour. Med. Sc., 1916, xlii, 28.
[12] Blumer: Yale Med. Jour., 1911, xviii, 153.

was curetted from the site of injury by Dr. George D. Stewart, perfect bony union resulted, and the patient remains well four years later. There was no detectable growth in the thyroid itself. Microscopic examination of the material curetted from the humerus showed a richly vascular tumor, the unit of which was an acinus structurally identical with that of the thyroid gland. The question naturally arose as to whether the bone lesion represented proliferation of thyroid tissue aberrant in the humerus or whether it was a metastatic growth from a clinically indetectable thyroid tumor. Rests of thyroid tissue in the bones have not, as far as I know, been described, and their presence in that situation is entirely presumptive. On the other hand, cases are by no means unknown in which bone metastasis with removal of the thyroid has failed to show neoplasmic growth in the latter, and, conversely, minute thyroid tumors have been known to occasion innumerable secondary growths in the osseous system and elsewhere.

In other circumstances the thyroid carcinomata are not beneficently inclined. In the case of a woman, aged fifty-eight years, who complained of right-sided hemicrania of four weeks' duration, percussion showed tenderness over the anterior portion of the right parietal region, and the thyroid was slightly enlarged and nodular. Dr. Van Horn Norrie made the diagnosis of cancer of the thyroid with metastases in the skull. Two weeks later the patient developed a mass corresponding to the area of tenderness in the parietal region. The mass grew rapidly. Autopsy revealed a carcinoma of the thyroid with infiltration and destruction of the right parietal and adjacent temporal bone, two small nodules in the liver, numerous metastases in the lungs, and a solitary nodule in the right supraclavicular fossa.

In the Bellevue Hospital autopsies the marrow of one or more bones was metastasized in 35 cases, or 11 per cent. The primary growths were as follows: carcinoma of the prostate 2, breast 10, stomach 6, thyroid 2, tail of pancreas 2, cancer of an aberrant salivary gland and of the jejunum 1 each, hypernephroma of the kidney 6, spindle-cell sarcoma 3, melanoma 1, and myelogenous sarcoma 1.

The vertebral column was involved twenty-five times. In the metastases from the prostatic growths the bones showed sclerotic changes, while in the breast, stomach, and other tumors the lesions in the bones, with a single exception, were destructive, in several instances permitting spontaneous fracture of the extremities or displacement of the vertebræ, with pressure upon the cord. The ribs were metastasized sixteen times, and in 8 of these there were companion lesions in the vertebræ. The bones of the skull were metastasized nine times, the sternum four times, the femur and pelvic bones three times each, and the humerus twice.

ESOPHAGUS. There were 23 cases of epithelioma of the esophagus, and in 9 of them the liver was metastasized—three times in association with growth in the upper end, three times in the middle, and three times in the lower portion. It is interesting to observe that in all 3 cases of epithelioma of the upper end of the esophagus the metastases in the liver were large and numerous. In 1 case the liver weighed 5680 gm., and in another 8449 gm. In the remaining 6 cases the secondary growths in the liver were either solitary or limited in number and size.

The perigastric lymph nodes were infiltrated in 10 cases, the periesophageal nodes nine times, the lungs and pleura seven times, the mediastinal nodes three times, the cervical nodes twice, and the heart once. The thyroid was twice invaded by direct extension, and the walls of the aorta, a bronchus, and the trachea once each.

STOMACH. From the stand-point of the pathologist the two outstanding varieties of carcinoma of the stomach are the medullary adenocarcinoma, springing from fully developed gastric tubules, and the adenocarcinoma arising on the basis of newly formed or regenerated tubules in the immediate vicinity of an old peptic ulcer. As far as their metastases are concerned there are certain differences between the two which are not without practical significance.

In the Bellevue Hospital series of autopsies there were 46 examples of medullary cancer of the stomach. Eight, or 18 per cent., were not accompanied by metastases, although the primary growths involved an extensive sweep of the stomach wall. In 1 case there was a solitary metastasis in the liver, in 15 cases, or 33 per cent., there were a few small metastatic deposits in the liver, in 3 cases the liver was the seat of numerous metastases, and in 19 cases or 41 per cent., the liver was free.

There were 22 instances of carcinoma of the stomach associated with preëxisting ulcer, and in 10, or 46 per cent., the liver was greatly enlarged and riddled with metastases, in 1 case it was the seat of a large solitary metastasis, in 9 cases, or 40 per cent., there were no metastases in the liver, and in 2 cases the growth was confined to the stomach. In all of the cases the primary growth was small, rarely exceeding a few centimeters in diameter. In other words a carcinomatous lesion of the stomach growing on the basis of an old ulcer may be insignificant in size and yet give rise to numerous and extensive metastases, particularly in the liver—an argument in favor of early eradication of the so-called healed ulcer with its circumferential zone of regenerated and immature epithelial tubules.

INTESTINES. There were 32 examples of carcinoma of the intestines as follow: duodenum 3, jejunum 1, cecum 10, ascending colon 2, splenic flexure 3, sigmoid 6, rectum 7.

The duodenal cancers were all formed on the basis of healed ulcers, and all of them were attended by extensive metastases, particularly in the liver and regional lymph nodes. In one of the cases the skin, pancreas, rectus muscle, thyroid, trachea, heart, liver, adrenals, kidneys, and dura were metastasized, which is not only an extensive but an unusual distribution. The case of carcinoma of the jejunum was likewise founded on the basis of a healed ulcer, and gave rise to extensive metastases in the pleura, lungs, mediastinal, mesenteric and thoracic and cervical nodes, and in the liver and vertebræ.

Of the 10 carcinomata of the cecum 5 were unattended by metastases, in 2 cases the pericecal nodes were alone metastasized, and in 3 cases infiltration of the pericecal nodes was associated with secondary nodules in distant parts.

Of the 5 colon carcinomata 2 were free from metastases, and 3 were associated with fairly extensive involvement of the regional nodes and of distant organs.

Of the 13 cases of carcinoma of the sigmoid and rectum, 8 were unattended by metastases, and 5 were associated with involvement of the regional nodes and distant organs.

Of the 28 cancers of the lower intestinal tract 15, or 53.5 per cent., were unattended by secondary growths. This is in striking contrast to the high degree of malignancy displayed by tumors of the stomach and of the upper intestinal tract.

Cardiac and Skeletal Muscle. There were 12 cases of muscle involvement. In 9 instances the heart muscle was affected and in 3 the skeletal muscles. In 3 of the cardiac cases direct infiltration arose from mediastinal lymphosarcomata and nodular metastases occurred 5 times—1 from a cancer of the duodenum, 1 from a spindle cell sarcoma of the humerus, 1 from an epithelioma of the esophagus, 1 from an adrenal hypernephroma, and 1 in a case of melanomatosis.

Th skeletal muscles showed nodular metastases three times only. There was a small solitary metastasis in the right rectus derived from a cancer of the duodenum, a single nodule in the right deltoid from a spindle-cell sarcoma of the sole of the foot, and several small nodules in the diaphragm from a primary cancer of the liver.

Thyroid. There were 12 cases of metastatic involvement of the thyroid gland. In 3 instances there was direct extension from primary esophageal growths, and in 2 cases the thyroid metastases were but the local expression of tumor dissemination. Of the remaining 7 cases the secondary growths in the thyroid were nodular in character, and were derived from carcinoma of the duodenum, breast, and stomach once each, and from hypernephroma and sarcoma twice each.

Skin, Subcutaneous Tissues, and Lymph Nodes. Enlargement of the superficial lymph nodes often occurs in association with

malignant growths, and the question then arises as to whether the secondary process is metastatic or due to lymphoid hyperplasia dependent upon absorption from ulcerative areas, or upon reactive hyperplasia of the endothelial cells of the lymph sinuses. In any event, determination of the nature of the secondary process is of importance from the stand-point of both prognosis and treatment. In the same way histological investigation of secondary enlargements in the skin or superficial nodes is occasionally of great assistance in determining not only the nature and sometimes the location of deep-seated growths, but the method of treatment. Thus, in a case which came under my observation at the New York Hospital some years ago a solitary nodule removed from the region of the scapula revealed a new growth which strongly suggested metastasis from an adenocarcinoma of the stomach, and the institution of palliative operative procedures based on this finding confirmed the suspicion. In another case, in the same hospital, removal of a small nodule from the head of the fibula resulted in the discovery of a hypernephroma of the kidney.

In the Bellevue Hospital series there were 11 cases, or 3.7 per cent., in which enlargement of superficial structures depended upon metastasis from deep-seated growths. In a case of cancer of the duodenum there were several small nodules in the skin of the abdomen, back, shoulders, and scalp; there were 3 cases of enlargement of a solitary supraclavicular node in association with deep visceral cancers, and 2 instances of axillary involvement, in a case of hypernephroma of the kidney there was a small nodule in the skin of the chest, and, in a second case, a nodule beneath the scalp, and in 2 cases of epithelioma of the upper end of the esophagus there were nodules in the cervical region.

In still another case there were innumerable nodules in the skin, and microscopic examination of one of them during life showed histological changes scarcely to be differentiated from those of a neurofibroma. At autopsy, however, a small scirrhous cancer of the stomach was found, and examination of numbers of skin nodules from various parts revealed localized areas of sclerosis in the subcutaneous connective-tissue embedded in which were minute alveoli of cancer cells representing metastases from the growth in the stomach. In view of the histological changes observed in the skin during the life of the patient, and because of the number and distribution of the nodules and their painful nature, the case was regarded clinically as an example of von Recklinghausen's disease (neurofibromatosis universalis).

SUMMARY AND CONCLUSIONS. 1. Slightly less than 6 per cent. of all patients dying in Bellevue Hospital and coming to autopsy are subjects of malignant disease.

2. Of 298 malignant tumors observed postmortem at Bellevue Hospital, 220, or 74 per cent., were attended by metastases. The

lymph nodes, liver, pleura and lungs, bones, and adrenals were the organs most commonly metastasized, and they were involved in the order named.

3. Epithelial tumors predominated over those of connective-tissue origin in the proportion of 8 to 1.

4. As far as the process of metastasis is concerned, the organs of the body are divisible into 3 groups: (1) A group made up of organs which are frequently the seat of metastasis, but in which primary growths are exceedingly rare; (2) a group composed of organs which are more or less commonly the seat of primary growths, but which are themselves rarely metastasized. For example, the lymph nodes, liver, lungs, pleura, and bone marrow give rise to malignant growths only rarely, but metastasis to these organs is common, while the stomach, breast, pancreas, prostate, etc., frequently give rise to malignant tumors, but are themselves seldom metastasized. Finally there is a third group of organs the members of which are neither the seat of frequent tumor growth nor of metastasis, namely, the spleen, heart and skeletal muscle, kidney, thyroid, etc.

(*a*) Splenic metastases are of rare occurrence and are practically always small in both size and number. They are frequently associated with numerous metastases in other situations. From this it seems reasonable to infer that metastasis of the spleen is late in point of time and that it follows only after frequent and persistent visitation of tumor cells to the splenic sinuses. Further evidence that the spleen is antagonistic to the growth of metastatic deposit is afforded by the fact that in 3 cases of carcinomatosis and in one of melanomastosis the spleen was free from detectable sign of involvement, although, in company with every other organ in the body, it must have received an abundance of cells whose vegetative capacity was in no wise different from those delivered to and successfully inoculated in other parts. The conclusion, it seems to me, is justifiable that the inimical attitude of the spleen toward the growth of metastases is dependent upon resistence inherent in the splenic cells, reënforced, perhaps, by lytic properties in the blood of the splenic sinuses. No doubt the same argument is applicable to other organs in which metastases are infrequent and small, notably, the kidneys, thyroid and muscles.

(*b*) Metastatic involvement of muscle tissue is a rare event. A new growth may abut directly on the muscle and destroy it as a result of pressure, but infiltration of tumor cells between muscle fibers is not common, and nodular metastasis is almost unknown. On the other hand the movement of tumor emboli along the intramuscular lymphatics is frequent enough, and their passage is probably facilitated by mechanical conditions, although there are many muscles whose activity is reduced to a minimum in cachectic subjects—in fact, conditions in them are equivalent to rest, and yet metastasis is almost unknown. Whether there is a

substance produced by the muscle itself that serves as an additional obstacle to the deposition and growth of tumor cells is a question.

(*c*) The kidney, although seldom metastasized, appears, relatively speaking, to be a favorite seat for the lodgment of metastases from sarcomata. Carcinomatous metastases in the kidney are rare and are small in size and number, seldom exceeding a few millimeters in diameter nor more than a half-dozen, and are practically always found in the cortex.

5. The great majority of all splenic metastases are derived from tumors which are notorious for metastasizing to bone marrow—cancers of the stomach and breast, and hypernephromata—a fact which assumes additional interest when it is recalled that there is a structural resemblance between bone marrow and the splenic pulp.

6. Both adrenals were completely or almost completely destroyed in 65 per cent. of the total number of neoplasmic lesions observed in them. In not one of the number was pigmentation of the skin or mucous membranes observed at autopsy, nor were these or other signs of Addison's disease detected during life.

(*a*) The suprarenal capsule, like the kidney, is a favorite site for the lodgment and growth of sarcomatous metastases, the proportion of epithelial to connective-tissue metastases being only 3 to 1.

7. Neoplasmic invasion of the larger veins, with or without subsequent thrombosis, is uncommon, and occurred only thirteen times, or in 4 per cent., of the Bellevue Hospital series. The hypernephroma shows the greatest avidity for the vessels, 7 out of 15 cases, or 46 per cent., having produced secondary lesions in the veins. Suspicion should be directed to neoplasmic thrombosis of the portal vein in rapidly developing ascites, and to similar changes in the common iliac vein in edema of the lower extremity, when the physical signs in question are otherwise inexplicable.

8. The so-called Krukenberg tumor is not primary in the ovary, but in the stomach, where it springs, most likely, from the parietal cells of the fundus glands (Hall, Symmers). The ovarian manifestations are purely metastatic, and are apt to be bilateral.

9. Cancer of the stomach, occurring on the basis of regenerated epithelial tubules at the periphery of an old peptic ulcer, may be insignificant in size and yet give rise to innumerable and widespread metastases, whereas the medullary cancer, which appears to spring from mature gastric tubules, is apt to attain enormous dimensions, showing, at the same time, a noticeable tendency to remain confined to the stomach. In fact, it seems probable as a general proposition, that adenocarcinomata that arise on the basis of regenerated epithelial structures, such as are constantly seen around old gastric ulcers and in chronic hyperplastic gastritis, metastasize earlier and more extensively than those which spring from an apparently normal mucosa. Thus, the adenocarcinomata of the breast occurring in associa-

tion with chronic productive mastitis and attended by compensatory regeneration of epithelial acini, and those cases which follow lactation hyperplasia, are among the most malignant of all known varieties of cancer of the breast. The adenocarcinomata of the gall-bladder associated with regenerative efforts on the part of the mucosa to repair lesions mechanically produced by gall-stones, are exceedingly malignant, and give rise to extensive metastases and to early involvement of contiguous structures. Carcinoma of the prostate is practically always associated with histological changes indicating neoplasmic transformation of regenerated epithelial tubules occurring in association with chronic interstitial prostatitis, and the same is true of carcinoma arising on the basis of adenomatoid hyperplasia of liver cells in cirrhosis. On the other hand, carcinoma springing from apparently mature tubules, or in situations where cells are protected from injury, are apparently less active in the matter of producing secondary growths. The explanation, I think, lies partly in the fact that regenerated tubules often approach the fetal type of architecture, and in them the function of growth is a prominent if not a dominant feature, whereas tumors springing from apparently mature epithelium are composed of cells not so markedly consecrated to assimilation and reproduction, such, for example, as the colloid-producing cancers of the thyroid, the milk-producing cancers of the breast, etc.

10. Of 28 cancers of the lower intestinal tract, 15, or 53.5 per cent., were not accompanied by infiltration of surrounding structures or by metastasis. This is in striking contrast to the high degree of malignancy shown by tumors of the stomach and upper intestine.

I wish to acknowledge, with thanks, assistance rendered by Dr. E. E. Stern, of the interne staff of Bellevue Hospital.

THE DIFFERENTIAL DIAGNOSIS OF MEDIASTINAL CONDITIONS.

By A. McNiel Blair, M.D.,
SOUTHERN PINES, N. C.

Anatomically the mediastinum is divided into an anterior position lying in front of the roots of the lungs and a posterior position behind them, the two being continuous; but since the use of the roentgen-rays and perfected fluoroscopic examinations (by placing the patient in a right oblique anteroposterior position), clinically three distinct mediastinal spaces are made apparent, and are called the anterior, medial, and posterior.

The anterior mediastinal space contains the lymph nodes, the areolar tissue, and the thymus or its remains. The medial and

posterior contain the heart with its afferent and efferent vessels, the trachea, the bronchi, the esophagus, thoracic duct, vagus, phrenic and sympathetic nerves, and lymph nodes.

As thoracic aneurysm is frequently the cause of sudden death referred without autopsy to other causes, and is more common than was once supposed, the condition being so often overlooked, I will dwell more especially upon thoracic aneurysm, using it as a working basis from which the differential points of diagnosis of mediastinal conditions generally may the better be brought out, in view of the common symptomatology of mediastinal conditions in general.

When the walls of an artery become diseased singly or *en masse*, with a resulting dilatation, we have a condition called aneurysm; therefore a true aneurysm represents a more or less localized dilatation of an artery, due to the weakening effect of a chronic degenerative arteritis, syphilis standing first as the cause of a large majority of the cases.

Intemperance in eating and drinking, physical and mental overwork or overstrain may act as contributory causes, the first symptoms often arising after severe or prolonged muscular effort. Some authors describe "dating of symptoms" from trauma, such as severe falls or railroad accidents. It is not improbable, however, that a congenital weakness of the vessels existed primarily, due to inherited process, traceable to one of the factors before mentioned.

Greene states: "Roughly speaking, three-fourths of all aneurysms are aortic; nineteen-twentieths of these are found in the thoracic aorta; of these 90 per cent. are sacular; from 80 per cent. to 90 per cent. occur in the male, and 50 per cent. occur between the ages of thirty-five and fifty." The chief points of attack are the root of the aorta, the junction of the ascending and transverse portions, and the descending arch, in the order indicated.

First let us consider the anatomical arrangement. The arch consists of three portions: the ascending, the transverse, and the descending. The ascending lies behind the pulmonary artery, at the level of the third costal cartilage, being separated from the sternum by the pericardium only, which covers it for about 5 cm.; therefore, aneurysms existing in the ascending portion may rupture into the pericardial cavity.

The transverse portion of the arch passes from a point corresponding to the first right interspace, directly backward into the mediastinum, to the left of the vertebral column, giving off three branches: the innominate, the left common carotid, and the subclavian arteries.

The descending or thoracic aorta begins at the third dorsal vertebra and passes along the median line to the aortic opening in the diaphragm.

Look for a moment at the cross-section of the chest and consider "that a transverse line touching the anterior surface of the bodies of the dorsal vertebra lies about the middle of the anteroposterior

diameter of the thorax," and as the symptoms are dependent upon size, site, and direction of the growth of the aneurysm, the condition may remain latent even with large dilatation, or may be manifested by distinct pressure effects, with or without external physical signs. It may grow forward to the sternum, eroding the latter, appearing as a pulsating tumor just at the manubrium or to the left of it.

"The arch being in close contact behind, with the trachea, esophagus, thoracic duct, and left recurrent nerve, which winds around it; all these may be compressed by the growth or it may burst into the trachea or esophagus, causing fatal hemorrhage."

The orifice of one of the large branches may be closed by atheromatous changes, causing a disappearance or delay in the radial pulse on the corresponding side. This brings us to the old classification: (*a*) aneurysms with signs but no symptoms; (*b*) aneurysms with symptoms but no signs; (*c*) aneurysms with neither symptoms nor signs.

The so-called classical symptoms, we are told, develop only in certain cases, usually when terminal stages have been reached, and in these cases the diagnosis is comparatively easy. But what about the remainder of these cases, in which wrong diagnoses simply permit of the further shortening of the already shortened term of life allotted to this class of sufferers?

The usual symptoms complained of by the patient are pain, precordial oppression, difficulty in breathing, and feelings of general weakness, along with one or more of the predominant pressure phenomena.

Behan, in his book on *Pain*, in speaking of the pain in aneurysm, describes it as constant and gnawing, as a rule. In some cases it is paroxysmal, though often in the early stages it may be entirely absent. In many cases the patient locates the pain over the tumor mass by pressing over the affected area with his hand. A characteristic of the disease is that deep pressure is always grateful.

The pain above described as gnawing, boring, etc., is caused by pressure upon the chest wall, while upon the sensory nerves the pain is referred to their peripheral distributions. These referred pains vary with the situation of the tumor.

Aneurysms of the thoracic aorta, however, do not produce so much pain as do those of the abdominal aorta. In all cases of suspected aneurysm, careful inquiry should be made as to the presence of pain, because the patient frequently neglects to mention it.

The pressure phenomena have been ingeniously classified as follows:

1. Pressure upon the esophagus results in dysphagia.

2. Upon the trachea, pressure causes the brazen cough (gander cough), also dyspnea, stridor, bronchorrhea, and hemoptysis even without rupture of aneurysmal sac.

3. Upon the root of the lung and pleura, pressure leads to deficient

lung aëration, with symptoms suggesting phthisis and pulmonary collapse, *e. g.*, case cited by Dr. John Pryor, during his service with Professor Koch. The patient responded to tuberculin reaction, but died ten days later, and autopsy showed a ruptured aneurysmal sac.

4. Pressure upon the nerve trunks results in the neuralgic type of pain, being paroxysmal and intermittent.

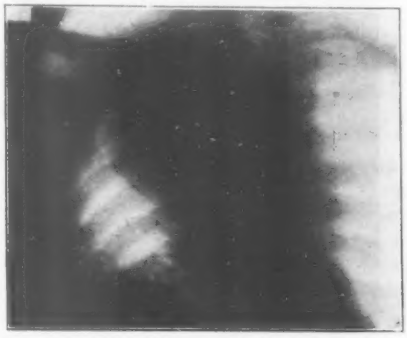

FIG. 1.—Aortic aneurysm. Mr. G., aged thirty-six years. Luetic history positive. Blood-pressure reading: right, 125–110; left, 115–95. Characteristic physical signs but no symptoms.

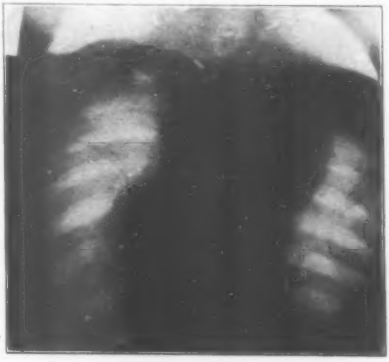

FIG. 2.—Aortic aneurysm. Mr. C. P. Y., aged fifty years. Luetic history positive. Blood-pressure: right, 125–90; left, 110–60. No characteristic physical signs, except delayed left radial pulse. Expiratory type of dyspnea, with excessive localized sweating. (Negative is shown reversed.)

A point of difference in the pain of aneurysm and aortitis is exemplified in Figs. 3 and 4. In this particular patient the pain was localized at the right of the third costal cartilage and over the middle portion of the manubrium, and was referred to the back of the

neck and over the shoulders, shooting to the back of the head. It differed from the description of aneurysmal pain, in that it was sudden in its onset, occurred often in the epigastrium, and resembled angina pectoris in severity and suddenness. Paroxysms lasting only

FIG. 3.—Miss McC., aged sixty-three years. Blood-pressure, 150–125. (See text.) In this case anginal type of pain experienced, with unusual distribution, and emphasizes Behan's description of difference in the type of pain in aortitis from that of true aneurysm. Patient died suddenly, during apparent convalescence, from lobar pneumonia.

FIG. 4.—Miss McC., aged sixty-three years. Abdominal findings in Fig. 3, with aortitis and aortic dilatation.

a few minutes were often produced by exercise and ingestion of food, and elevation of arterial pressure when accompanied by contraction of the peripheral superficial vessels.

5. Pressure upon the pulmonary artery gives a systolic murmur, due to primary hypertrophy of the right ventricle, with subsequent dilatation of right ventricle.

6. From the sympathetic pressure we have dilated or contracted pupils, unilateral sweating, or pallor.

7. From pressure on the cardiac plexus, the anginal attacks.

8. While edema of the upper extremity and cyanosis come from the superior vena cava pressure.

9. Loss of flesh usually occurring in these cases, the resulting marasmus might readily be traceable, in part, to pressure upon the thoracic duct.

10. While the vagus interference could result in dyspepsia, nausea, vomiting, dyspnea, and hiccough.

11. Unilateral paralysis results from the phrenic pressure.

12. While hoarseness, aphonia, spasm or paralysis of the left vocal cord and paroxysmal dyspnea come from pressure on the recurrent laryngeal nerve. This classification of pressure symptoms applies to mediastinal growths in general, including aneurysms.

It is hardly necessary to go over the physical signs in detail; I wish only to touch upon certain points.

Inspection is very important. The manubrium and the back, between the left scapula and the spine, should come in for special scrutiny.

A visible tumor, yielding expansile pulsation, is rarely met with. The peripheral signs of associated aortic regurgitation may be present. Cardiac hypertrophy, as indicated by the apex beat, is commonly but not invariably associated. Atheromatous changes in peripheral vessels; cyanosis, localized edema; unequal pupils, vasomotor symptoms, stridor, visible dyspnea; paralysis of the vocal cords associated with hoarseness or aphonia; and brazen cough are all recognized by aid of inspection.

In palpation one seeks to elicit the expansile pulsation and thrill and the so-called diastolic shock.

Tracheal tugging, described by Oliver, has been met with in so many cases other than aneurysm, and has been absent when aneurysm actually existed, that it is not so important as we were once taught, for example, in a case of adhesions of the left pleura (Fig. 5) this physical sign was in evidence. The palpation of the radial pulses and carotids, for comparison, is very important.

In aneurysm of the ascending portion of the arch involving the innominate the right radial and carotid are affected; in the descending portion, the left radial. A delayed pulse may accompany aneurysm of the transverse portion.

As to percussion, auscultatory percussion is by far the more reliable, and may be further checked by use of the tuning fork, as auscultatory findings are not constant factors, owing to coexisting or associated valvular disease. One can hear at times a systolic

bruit, often harsh, vibrant, and associated with palpable thrill, coming from or produced by the sac itself.

A localized systolic murmur heard at the left back is given as an important sign. A distinct ringing metallic second sound heard, not over the aortic valve itself, but over the sac, is given by Greene as a

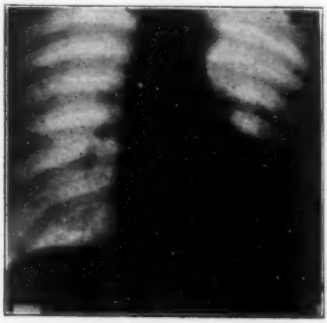

FIG. 5.—Mrs. J. L. R., aged fifty years. Negative Wassermann. Marked cardiovascular symptoms. Blood-pressure, 164–140. Tracheal tug. Present condition shown to be due to left pleural adhesions and thickening, with mechanical traction accounting for aortal symptoms.

FIG. 6.—Miss L., aged twenty-one years. Tuberculosis of bronchial glands only; showing type of mediastinal infiltration in this class of cases.

most important sign. It should be added that much is to be learned from systematic blood-pressure readings, not from one arm only but from both, and compared. The systolic as well as the diastolic readings are necessary, as the variation of the pulse-pressure on the two sides is most important. And last, but not least, often the fluoro-

scopic and roentgen-ray examination offer the only means of an early diagnosis at our command.

DIFFERENTIAL DIAGNOSIS. Mediastinal abscess is differentiated by its rapid development with symptoms of suppuration, and absence of aneurysmal symptoms other than those from pressure.

FIG. 7.—Dr. J. W. B., aged forty-seven years. Sarcoma of the mediastinum; left-sided glandular involvement of the sublingual, submaxillary and cervical glands, along with tongue involvement. Case strongly resembled Hodgkin's disease. (Negative is shown reversed.)

FIG. 8.—Miss E. M. E., aged forty-five years. Blood-pressure, 145-110. Bronchial asthmatic dyspnea included because of cardiovascular symptoms in the case. Bronchial glands, with dilatation of the bronchi contributory factors.

Pulmonary fibrosis, or any case involving the retraction of the lung, may give rise to suggestive pulsation in aneurysmal areas; but ordinary methods reinforced by fluoroscopic examination of the arch will exclude this condition.

Pulmonary tuberculosis, with large cavity, adjacent to aneurysmal areas, may produce pulsation and certain aneurysmal signs, but history, sputa, breath sounds, etc., should prevent error.

Anemic pulsations can be readily differentiated.

FIG. 9.—Mr. L. P. S., aged sixty-three years. Cardiac hypertrophy and aortic dilatation chronic. Symptoms of decompensation; no pain; dyspnea marked; gastro-intestinal disturbance. Sudden death.

FIG. 10.—Mr. W. J., aged seventy-one years. Senile aortic dilatation presenting itself in the course of cardiac hypertrophy associated with interstitial nephritis.

Malignant growths in the mediastinum are best differentiated by means of the roentgen-rays. In their absence, knowledge of primary focus of malignant growth, absence of auscultatory signs of aneurysm, rapid emaciation, absence of expansile pulsation should be of material help in differentiation.

The coexistence of the two conditions, malignant growth and aneurysm, have been reported.

Growths of the mediastinum may call for differentiation. Goodkind speaks especially of those which may originate:

(1) Primarily from structures within the mediastinum; (2) from contiguous organs, growth of which may encroach upon the mediastinal space (lungs, pleuræ, and thyroid); (3) metastatic growth from distant organs (breasts, gastro-intestinal tract, especially rectum, uterus, prostate, and kidney); (4) Hodgkin's disease and the leukemias.

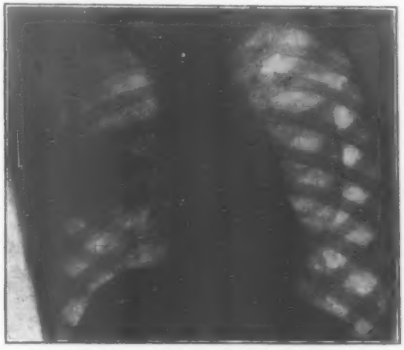

FIG. 11.—M. H., aged thirty-six years (colored). Wassermann positive. Gummatous formation in the mediastinum (cystic) and gumma in the right middle lobe; no pain. Stridulous type breathing; expiratory type of dyspnea; aphonia; emaciation.

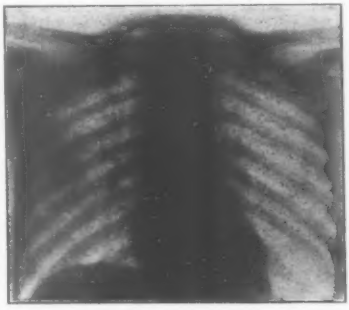

FIG. 12 —M. H. (colored), showing effects after two months of antiluetic treatment

Among the rarer forms he also mentions fibromas, lipomas, myomas, etc., and gummas. He points out that the more common growths of the mediastinum are, however, sarcomas and carcinomas, and emphasizes the fact that aneurysms may simulate mediastinal growths. As to differential diagnosis of the latter, he states that the general symptoms are those common to malignancy: weakness, loss of weight, secondary anemia with a progression to complete marasmus.

Local symptoms are dependent upon the structures compressed. Dyspnea is the most common. Pain is usually dull, of aching type, and may be located quite remote from the neoplasm.

With growths in the posterior mediastinum, causing compression on the emerging nerve roots from the vertebral column, severe pain may be present in the back or along the lateral chest wall.

In a recent article, Guttman and Neuhof[1] offer the following explanation of the marked difference in the two brachial blood-pressures, and in the two radial pulses, in conjunction with laryngeal paralysis, which so closely resembles the clinical syndrome of aortic aneurysm: "That the dilated pulmonary artery was probably wedged in with sufficient force under the aortal arch, and especially opposite the origin of the left subclavian artery, as to cause interference with the circulation of the latter and consequent difference between the two sides in the brachial blood-pressure and in the radial arteries."

The extrabronchial causes of tracheobronchial stenosis, according to Lord,[2] require differentiation.

These extrabronchial causes comprise, for the most part, diseases which develop in or about the mediastinum or invade this region, as in a case of malignant disease by metastasis. They may also give indication of their presence by the aneurysmal syndromes before mentioned, *i. e.*, by dulness in the supracardiac region or over the vertebra between the third and ninth dorsal spine and such signs of pressure upon other organs as dysphagia, inequality of the pupils, or the pulses, variation in the blood-pressure in the two arms, "tracheal tug," recurrent laryngeal paralysis, engorgement of the vessels of the head or neck or one arm, and dilated superficial thoracic veins.

The history of syphilis, attacks of pain like angina pectoris, pulsation of the dull area, systolic thrill and murmur, diastolic shock, and aortic regurgitation speak for aneurysm.

Cachexia and enlarged cervical or axillary glands suggest malignant disease.

Mediastinal involvement in a child with tuberculosis is likely to be due to enlarged and tuberculous glands.

Examination with the roentgen rays is important and may lead to the detection of extrabronchial disease, of which there is no indication on physical examination.

Syphilis of the lung, more especially in reference to gummatous formations, may simulate aneurysm. Such a diagnosis may be based on: (*a*) Knowledge of syphilitic infection followed by secondary manifestations and the coexistence, with the pulmonary processes, of other tertiary syphilitic lesions; (*b*) ulceration or stenosis

[1] Radial Pulse Difference and Left Recurrent Nerve Paralysis Due to Mitral Stenosis, Jour. Am. Med. Assn., January 29, 1916, p. 336.

[2] Diseases of the Bronchi, Lungs, and Pleuræ.

of the trachea or bronchi, wherein is suggestive evidence; (*c*) positive Wassermann reaction; (*d*) the roentgen-rays.

As to gummas, according to Lord, these may be found in any part of the lungs, more commonly within than on the surfaces. Favorite sites for this lesion are the middle lobe of the right lung principally and in the hilum, and are usually without symptoms.

Cough and dyspnea are frequently met with; pain is rarely experienced. Emaciation may exist, with extensive pulmonary disease, as seen in diffuse fibroid induration.

It is to be noted in closing that the thymus gland may degenerate and undergo sarcomatous changes and may simulate aneurysm, thus calling for differentiation.

I wish especially to emphasize that there is no one single physical sign of aneurysm which may not be produced by other conditions than aneurysm. Moreover, it is extremely difficult to differentiate between a transmitted pulsation and a true expansile pulsation. The uniform method of checking all physical examinations of the chest in doubtful cases with the fluoroscope or roentgen-ray plates is to be commended as the only means which will lead to more accurate and early diagnosis of mediastinal conditions.

THE SIGNIFICANCE OF URETERAL TUBERCLE BACILLURIA.[1]

By Edwin Beer, M.D.,
NEW YORK.

(From the Surgical Service of Mount Sinai Hospital.)

The problem that I propose to lay before you tonight is replete with difficulties, and may be encountered by anyone who deals with patients suffering from urogenital tuberculosis. I fear that in this field very few categorical statements are permissible, and that in each individual case the surgeon will have to carefully weigh the evidence before arriving at the conclusion that he is dealing with a case of renal tuberculosis or not. In my experience with cases of genital tuberculosis this problem has been most complicated, and in a perusal of the scanty literature I find that others have met very much the same difficulties as I have encountered. A failure to properly interpret the clinical findings has repeatedly led clinicians astray and has suggested the belief that occasionally patients suffering from renal tuberculosis are cured by non-surgical procedures.

A brief review of the following published cases will illustrate

[1] Read before the Genito-urinary Section, New York Academy of Medicine, February 21, 1917.

some of the difficulties to which I wish to refer. In Kielleuthner's excellent paper[2] he cites two very instructive cases in which the interpretation of the findings, *i. e.*, the significance of ureteral tubercle bacilluria, is by no means clear.

CASE I (Israel).—In this patient the right kidney was recognized as tuberculous by all the usual criteria, including the presence of tubercle bacilli. The bladder was moderately ulcerated. In the urine from the left (second) kidney there was albumin, otherwise negative, but the guinea-pig inoculation was positive. What was the significance of this bacilluria? Did it signify renal tuberculosis of the second kidney? Did it point to an excretory bacilluria from a non-tuberculous but moderately impaired second kidney? or was it an accidental contamination of the ureteral specimens in the catheter's intravesical transit? As the patient was well three years later, one might suspect a spontaneous cure, though it is much more likely that the second kidney was not tuberculous and that the positive guinea-pig test was explicable by contamination or by an excretory bacilluria. The latter view of an excretory bacilluria is accepted by Israel and Kielleuthner.

CASE II (Kielleuthner).—In this patient the left kidney specimen was typical of renal tuberculosis (turbid, red and white cells, tubercle bacilli). The right kidney showed good indigocarmin output, clear urine, with small amount of albumin (0.4 per cent.), few hyaline casts, no microscopic elements. The guinea-pig inoculation was positive on both left and right ureteral specimens. The bladder was inflamed, bled easily, had diminished capacity, and showed several typical ulcers. Reëxamination with the greatest care, to avoid contaminations, washing "in and out" through the ureter catheters, gave the same result, guinea-pigs were positive on both sides. Two months after a left nephrectomy for tuberculosis a guinea-pig test on the bladder urine was still positive, and three months later a specimen from the right ureter was negative in an inoculation test. Subsequently reëxamination confirmed this; bladder urine still positive, but right kidney urine negative. The author believes this again illustrates an excretory bacilluria from the right kidney while the left tuberculous kidney was *in situ*, which bacilluria disappeared after nephrectomy. Unfortunately he ignores the fact that, despite the nephrectomy, a tuberculous focus, as proved by positive inoculation from bladder urine, was still in the urinary tract, from which we might expect a continued excretory bacilluria if his interpretation were correct. He also fails to state whether the albumin had disappeared from the urine of the remaining kidney, which, as we shall see, he believes is always present in the cases showing excretory bacilluria. Kielleuthner's interpretation of his facts may be correct, but his reasoning is not

[2] Folia Urologica, 1912–1913.

convincing. A contamination, despite great care, of the ureteral catheters in transit through a diseased bladder, as well as a reflux up the healthy ureter, which might produce a contamination, must also be considered as likely sources of the tubercle bacilli that led to the repeatedly positive guinea-pig tests on the healthy side.

CASE III (Bottomley-Cunningham[3]).—In this male patient the diagnosis of right kidney tuberculosis based upon ureteral specimen inoculation tests was made in 1907. A characteristic unilateral genital tuberculosis, going on to abscess formation, was also present. After eighteen months' tuberculin treatment the symptoms (?) were entirely absent, and two years ago (1914) inoculation tests of the urine were negative.

This case might furnish comfort to those who believe that renal tuberculosis might be cured by tuberculin, though the author avoids making any such claim. The question that interests us is, What was the significance of the ureteral tubercle bacilluria on which the diagnosis of right renal tuberculosis was based. It is remotely possible that there was a renal tuberculosis and that hygiene, tuberculin, etc., effected a cure. Until we are sure that the specimens were not contaminated by tubercle bacilli derived from the genital tuberculosis, either by being picked up in the instrument or the catheters, or by reflux up the ureters, or by excretion through a non-tuberculous kidney, the original diagnosis must be looked upon with skepticism.

CASE IV (Brown[4]).—Male, aged twenty-eight years, consulted a physician for eugenic purposes before marriage. His urine contained albumin, and a specialist found tubercle bacilli in the urine from the right kidney. A second specialist could not corroborate these findings, but suspected that the diagnosis of right renal tuberculosis was correct. While under hygienic therapy the sediment of his bladder urine was inoculated into guinea-pigs, with negative results. He gained in every way, and six months later developed a tuberculous epididymitis, which was removed. Then the suspicion that the right kidney was tuberculous was again entertained.

From the few data in the case report, renal involvement cannot be excluded. On the other hand it is not at all unlikely that the genital tract may have been diseased at the first cystoscopy, and contaminations might have taken place.

From these brief preliminary remarks it must be evident that the significance of ureteral tubercle bacilluria is not as easily described as we would desire.

Tubercle bacilli may be present in ureteral specimens under three conditions, even though their presence usually indicates a renal tuberculosis.

[3] Surg., Gynec. and Obstet., October, 1916.
[4] Jour. Am. Med. Assn., March 13, 1915, p. 887.

I. When there is a tuberculous focus in some other part of the body and the bacilli are excreted from a non-tuberculous kidney.

II. When there is a tuberculous focus in the genital or urinary tract by contamination or by ureteral reflux.

III. When the tuberculosis is in the upper urinary tract or kidney.

I. A great deal of work has been done on excretory tubercle bacilluria, but much of it is almost worthless, as it lacks the completeness of careful scientific work. Moreover, much of the best work is partly contradictory.

Foulerton and Hillier[5] examined 18 cases of advanced chronic pulmonary phthisis and found by inoculation tests 9 positive tubercle bacillurias, using bladder urine. At autopsy 6 showed no urinary tuberculosis. In this paper the necropsy reports are so brief, and regularly omit all mention of the condition of the genital tract, that one must be loath to accept the data as published. All the more so as Cunningham,[6] in a more careful study, reports that in 66 cases with advanced pulmonary tuberculosis he obtained 6 positive inoculations. He then collected the urines in those 6 cases with ureteral catheters and failed to corroborate the earlier findings in 4 cases.[7] In one of the remaining 2 cases there was a genital tuberculosis which he admits as a possible source of the bacilli, while in the remaining case, owing to the patient's death, further study was impossible. (Autopsy refused.)

Opposed to this careful work of Cunningham, more recently Bernstein[8] and Brown[9] report 10 per cent. positive inoculations under practically the same conditions, but their observations are so incomplete that one cannot but hesitate to accept them as indicative of excretory bacilluria.

Kielleuthner[10] also contributed a careful paper on this subject. He studied only males with phthisis. In 13 such cases, with albumin-free urine, with complete genito-urinary macroscopic and microscopic autopsies, all inoculation tests were negative. In 11 similar cases with albumin in the urine and non-tuberculous urogenital tract 3 inoculation tests were positive. From these series he concludes that the tubercle bacilli do not pass normal kidneys, but that when the kidneys are impaired, as evidenced by slight albuminuria, the bacilli may pass and an excretory tubercle bacilluria may develop. In the cases (Nos. I and II) previously quoted he applied these facts to interpret the presence of the bacilli in the urine of the second kidney.

It would therefore appear that in advanced tuberculous lesions

[5] British Med. Jour., 1901, p. 774.
[6] Boston Med. and Surg. Jour., 1911, p. 872.
[7] Possibly clinically hidden cases of prostatic tuberculosis.
[8] New York State Med. Jour., 1914.
[9] Loc. cit.
[10] Loc. cit.

excretory tubercle bacilluria may occur, even though the incidence varies so greatly in the work of different careful students. In less advanced lesions, judging from the isolated cases published, this seems to be a much more unusual occurrence. Rist and Kindberg[11] report two positive inoculations with urine from a patient who at autopsy showed only a sclerosed apical lesion, from which in turn tubercle bacilli were obtained (inoculation test). Wildbolz[12] reports a patient who passed tubercle bacilli through a diseased stone-bearing kidney and showed no distinct evidence of tuberculosis in her other organs. After pyelotomy the urine became clear and a subsequent guinea-pig test (one and one-half years later) was negative. Records of other similar cases of excretory tubercle bacilluria associated with stone or with tumor have been published, but do not bear close scrutiny, as too many sources of errors are apparent.

II. How often a tubercle bacilluria (non-excretory) occurs in tuberculous lesions of the genital tract has not been studied sufficiently as yet. Cunningham[13] found bacilli in 15 per cent. (in smears) from expressed prostates in cases of tuberculosis of the epididymis.[14] In inoculation tests their presence would probably be more frequent. Without autopsy work it will be well-nigh impossible to answer this question accurately, as when bacilli are present in the bladder urine in such cases it will often be most difficult to prove without autopsy that the kidney or kidneys are not contributing to the bacilluria that is present. It is in just these cases that one finds the greatest difficulty in interpreting the significance of ureteral tubercle bacilluria. It would be interesting to know how often normal kidneys are removed in just this type of case when the diagnosis is based upon the finding of tubercle bacilli in the ureteral specimen. As I see it such specimens may obtain their quota of bacilli in three ways when the kidneys are not tuberculous:

(*a*) As an excretory phenomenon.

(*b*) As the result of reflux up the ureter of bladder fluid containing bacilli.

(*c*) As gross contamination of the cystoscope or catheters despite the greatest care.

(*a*) It is perfectly conceivable that with tuberculosis of the genital tract an excretory bacilluria may take place. There is no valid reason for denying this possibility if we admit the validity of the proof just referred to, in which more distant foci of tuberculosis lead at times to a tubercle bacilluria. Naturally one would

[11] Presse méd., 1914, p. 177.

[12] Nierentuberkulose, 1913.

[13] Loc. cit.

[14] In 51 cases he examined the bladder and kidneys and found the bladder involved in 16, one kidney involved in 9, both kidneys involved in 5. His data for such diagnoses are not given.

wish to apply a simpler explanation to this phenomenon; such an explanation as is offered by a reflux from the bladder up the ureter or by a gross contamination. Still, in spite of one's inclinations I believe such a possibility as excretory tubercle bacilluria from a focus in the genital tract cannot be absolutely denied.

(*b*) When we come to the other possible explanations I believe we are on safer ground. Recently, Kretschmer has again called attention to the possibility of a reflux from the bladder up the ureters and has published excellent roentgenographs showing this phenomenon. I have repeatedly proved this both by using colored solutions in the bladder and recovering same from the ureteral catheter *in situ* as well as by roentgenograms with argyrol. This phenomenon occurs with what appears to be normal ureteral orifices sufficiently frequently to throw doubt on the absolute purity of ureteral specimens. It might be avoided by emptying the bladder of all its fluid as soon as the ureters are catheterized, but even then it may be too late, as bladder fluid containing bacilli may already have entered the ureteral lumen. The presence of the catheter in the ureter appears to affect the complete closure of its lower end, in this way permitting a reflux. But even when no catheter is in the ureter this occasionally occurs, as I have recently shown in a patient presented before the New York Surgical Society[15] in an argyrol cysto-ureterograph.

(*c*) Moreover, in introducing the cystoscope if tubercle bacilli are present in the urethra as well as in the bladder, most painstaking washings may fail to get rid of all the bacilli and thus allow of contamination of the ureteral catheters in transit to the ureteral meati.

The Brown-Buerger cystoscope with its separated catheterizing system would seem best calculated to prevent such occasional contaminations, though some surgeons, for example Casper,[16] think that it is easy to prevent the introduction of tubercle bacilli that may be in the bladder into the ureters. This leads him to the conclusion that tubercle bacilli in ureteral specimens mean renal tuberculosis. Einar Key,[17] having experiences similar to mine, admits that in unilateral renal tuberculosis, vesical tuberculosis and prostatic tuberculosis, such contaminations may take place and can be in a measure controlled by using a special type of closed cystoscope (Dingel). With this instrument I have had no experience. My technic is the following:

To guard against these contaminations the bladder is thoroughly washed through the sheath of the cystoscope and then the catheterizing system, with pins in the catheters, is introduced. Only after the ureters are catheterized are the pins removed and only

[15] Ann. Surg., 1916, v: case of prostatic and ascending renal tuberculosis.
[16] Verhandl. d. Deutsch. Gesellsch. f. Urolog., 1911, p. 57.
[17] Hygiea, 1908.

the later specimens (third and fourth) are used for tubercle bacillus examinations and inoculations.

II. In addition to the two sources just mentioned the excretory bacilluria and that due to some kind of contamination, there is the common source of tubercle bacilluria, renal tuberculosis. With careful work the bacilli can be demonstrated in the smear in over 80 per cent. of the cases of kidney tuberculosis and in probably a higher percentage in inoculation tests. The greater sensitiveness of the guinea-pig test is admitted rather generally, and there is no doubt that it is a *sine qua non* of accurate work in the recognition of tuberculosis in the genito-urinary tract. For some time I was under the impression that a positive inoculation test or a smear from a centrifugalized ureteral specimen which showed tubercle bacilli pointed definitely to the diagnosis of renal tuberculosis. If, moreover, the slide showed some pus cells plus tubercle bacilli, despite good function, I believe I was justified in making the same diagnosis and recommending nephrectomy. In view of the experiences gathered in a series of 8 cases I have been considerably shaken in my earlier convictions. Three of these cases I have selected, as they illustrate the great difficulty presented in interpreting the significance of ureteral tubercle bacilluria.

The cases that I wish to report are arranged in definite sequence, based upon the lesser or greater probability of renal involvement. The first case, despite the fact that it has many of the ear-marks of renal tuberculosis, I am pretty well convinced has no such involvement; the second case is to my mind less definitely free from renal tuberculosis; while the third is so similar in many respects to cases of renal tuberculosis that I have not the hardihood to declare against that diagnosis. Though I am inclined to regard all three cases as tubercle bacillurias without renal involvement, I feel so insecure in my position that I am laying the facts before you for discussion. With the facts, such as they are, I am, however, convinced that nephrectomy is not indicated.

CASE I[18] (972).—M., aged thirty years. In March, 1916, patient began to have some discomfort in left side of lower abdomen. In April the left epididymis became involved.

May, 1916. Examination showed a fairly well-nourished man, with definite tuberculosis of left epididymis. The vas was normal. Nothing abnormal palpable by rectum except slight induration about the right vesicle. The urine was clear and brilliant, but became turbid after gentle pressure on the prostate. Examination of urine voided before palpation of prostate showed many pus cells, a few red blood cells and epithelial cells, numerous tubercle bacilli in small groups and isolated. After palpation of prostate and vesicles, in the turbid voided urine, the pus and red cells were

[18] Histories are abbreviated. The careful bacteriological work was done by Dr. H. L. Celler.

more numerous, and the tubercle bacilli were much more readily found.

There was no pain on urination and no frequency. No other evidence of tuberculosis was detected. There was no cough and no night sweats.

The patient was placed on hygienic treatment, sexual intercourse was interdicted, roentgenotherapy was applied to the epididymis and to the prostate.

June, 1916. Weight has increased nine and one-half pounds. Urine is clear and brilliant. Microscopic examination of centrifugalized specimen shows less pus and less tubercle bacilli. Despite roentgenotherapy the disease in the epididymis is extending.

October, 1916. Has had nine intensive roentgen-ray applications. Disease has involved the whole left epididymis. Urine is brilliant and there are no vesical symptoms. Tubercle bacilli are present in voided urine, also faint trace of albumin, many red cells, and few pus cells.

November, 1916. Cystoscopy showed normal bladder and normal ureteral meati. There was slight bulging over the position of the prostate. Three specimens collected from each kidney. The indigocarmin output was strong and equal in both sides. In the posterior urethra there was slight play of prostatic lobes. In left sulcus there was purulent discharge. No ulcers seen. After centrifugalizing kidney specimens no visible sediment was obtained on either side. Smears from the left kidney showed tubercle bacilli in fairly large numbers, a very few leukocytes and red cells. Smears from the right kidney showed no tubercle bacilli, but rather more white and red cells than on other side. Two guinea-pigs were inoculated[19] from the last specimen from each side. Those inoculated with the urinary sediment from the left kidney died in one week and showed no tuberculosis; those from the right kidney lived six weeks and were negative.

Rectal examination showed left half of prostate elastic and larger than right.

November 15. Removal of left testis for extensive tuberculosis of epididymis and adjacent testis. From this patient made an uneventful recovery, and after spending two weeks in the country, where he gained about ten pounds, a cystogram was taken to determine whether the left ureteral orifice was patulous or not. No ureteral ascent took place even when the patient strained against the tied-off urethra. The voided urine is still brilliant, though in the first glass there are a few flocculi. The catheterized bladder urine continues brilliant and clear. Its sediment contains tubercle bacilli and pus cells. There is no kidney sensitiveness and there are no vesical symptoms. Patient feels perfectly well (February, 1917).

[19] Intra-abdominally and in groin.

Remarks. What is the significance of the tubercle bacilluria in the specimen from the left ureter? Do they indicate left renal tuberculosis? are they the result of an excretory activity of a non-tuberculous kidney? or are they present as the result of a contamination or a reflux?

I admit that a renal tuberculosis cannot be excluded. The continued absence of all vesical symptoms of the equal function of the two kidneys as well as the brilliantly clear vesical urine suggest that the kidney is not tuberculous. Are we then dealing with an excretory phenomenon or a contamination? To differentiate between these two possibilities appears well-nigh impossible.

CASE II[20] (391–917).—M. J., aged thirty-five years. As a child he had a tuberculous infection of the knee; since then has had no further sign of any tuberculous disease. In 1912 the patient developed some vague pleural irritative signs at his left base, which cleared up slowly. Thereafter he developed a series of urinary symptoms that gave him considerable distress. He had marked pain at the end of urination, with increased frequency, and the appearance of blood. There had been no lumbar pains and no colic. He had never passed sand or gravel. Examination of his bladder urine obtained by catheter showed enormous numbers of tubercle bacilli. The slide which I examined was literally covered with Koch bacillus. Physical examination showed a young man without any pulmonary involvement. There was no kidney tenderness, and the kidneys were not palpable. His prostate was smaller than normal, the right half impressing me as slightly atrophic. The testes were normal. Cystoscopic examination was made under the impression that the patient was suffering from a secondary vesical tuberculosis, with a primary focus in the left kidney, to which I had ascribed the earlier symptoms at the left base.

March 1, 1912. Cystoscopy and ureter catheterization. Bladder mucosa was deeply injected in trigone down to the neck. Edema well marked here, and this area bleeds readily. No ulcers and no tubercles were seen. Both ureteral meati were small but normal in appearance, without any periureteral injection or edema. Both ureters were catheterized and almost clear urine was obtained. Left kidney: albumin, 0; urea, 1.3 per cent.; few red and pus cells. Right kidney: albumin, 0; urea, 1.5 per cent.; occasional red cells; very few pus cells. Within seventeen minutes there was a strong discharge of indigocarmin on both sides. Cultures from the bladder and from each of the kidneys were sterile. Careful search in slides from the kidney urines, carried out by three examiners, one of whom spent eight hours in the search, failed to show any tubercle bacilli. This might occur despite the presence of a renal tuberculosis, though

[20] Med. Record, October 11, 1913.

it was surprising in view of the myriads that had just been found in the bladder specimen, recovered at this examination.

Urine from both sides inoculated into guinea-pigs gave positive results.

After the cystoscopy the patient was kept in bed and the vesical symptoms gradually disappeared. Still, the bladder specimens contained tubercle bacilli, and my attention was naturally directed to the lower tract. I catheterized the bladder before and after gentle massage of the prostate and found what we took to be an increase of bacilli in the second specimen. This I regarded as presumptive evidence of local disease, and to test this conclusion, which was so opposed to my original interpretation, I decided to use the tuberculin test.

Under 1 mg. of tuberculin all the vesical symptoms returned—hematuria, pain, and increased frequency. At the same time there was a mild febrile reaction and locally the half of the prostate that I had regarded as atrophic became markedly tender for the first time. This reaction rapidly subsided and the patient was placed on therapeutic doses of tuberculin, with the result that all the symptoms of vesical irritation disappeared, and no tubercle bacilli or red cells were to be found in his urine during the next six months.

Until November, 1915, patient continued well and had no vesical symptoms. Throughout this time he states his urine has been clear, and I have seen it on and off and found it brilliant and absolutely clear. In November, 1915, a few months after his marriage, bladder irritability began anew and lasted one week. In January, 1916, another attack of bladder irritability, with burning pain at end of urination. Day frequency was normal and at night voided once. There was pressure in the perineum. The voided urine contained a few red cells, numerous pus cells, tubercle bacilli, and a faint trace of albumin. Patient went to the West Indies, discontinued sexual intercourse, and felt well until March, when he had another attack. In April, 1916, he was examined in another clinic, with the following results:

Cystoscopy showed "a trigone hyperemic and hypertrophied, with bits of adherent mucus but no definite ulceration. Both ureteral orifices were apparently normal. The specimen from the right ureteral orifice showed an occasional white cell, no tubercle bacilli. The specimen from the left ureter showed many pus cells and a few definite tubercle bacilli. The functional test showed 18 c.c. excreted from the right side, with 15 per cent. phthalein and 28 c.c. excreted from the left side in half an hour with 17 per cent. phthalein." Guinea-pigs inoculated from both sides were positive. On these findings the diagnosis of left renal tuberculosis was made and nephrectomy advised.

I saw the patient on April 25, 1916, when there was no kidney tenderness but slight tenderness over the prostate per rectum.

The first urine was clear but contained a few flocculi. The catheterized specimen was macroscopically clear, but contained pus cells and tubercle baciili. After gentle massage of prostate with the catheter in the posterior urethra, blood and frank pus were obtained.

Cystoscopy showed normal bladder except just behind the left ureter orifice and over a moderately bulging prostate, where two very small, probably traumatic, submucous hemorrhagic areas were visible. There was slight hyperemia about the right ureter orifice but none about left. The indigocarmin output was intense in sixteen minutes and equal on both sides. Rectal examination showed the right half of the prostate smaller than the left, and this smaller half was slightly tender. The bladder capacity varied from 12 to 19 ounces, and there was no frequency; no night urination.

The examination of the *bladder specimens* obtained at cystoscopy showed: albumin, a trace; urea, 0.9 per cent.; epithelial cells; many pus cells; moderate number of red cells, with tubercle bacilli in clumps.

The right kidney specimen showed: no albumin; urea, 0.9 per cent.; epithelial cells; occasional leukocytes; no red cells. No tubercle bacilli found.

The left kidney specimen showed faint trace of albumin, urea 1 per cent., epithelial cells, moderate number of white cells and small number of red cells, together with isolated tubercle bacilli.

Two guinea-pigs inoculated with sediment (centrifugalized) and with supernatant fluid from the right kidney developed tuberculosis. Of two guinea-pigs inoculated with sediment and with supernatant urine from left kidney, the former was positive and the latter negative.

Since this cystoscopic examination the patient has been under regular observation. He has no increased frequency nor nocturnal urination. His voided urine is brilliant but contains flocculi, while the catheterized bladder urine is regularly brilliant and clear, though the microscopic examination regularly shows pus cells and tubercle bacilli. Even after long centrifugalization there is only the slightest sediment. The patient has gained weight and feels perfectly well.

January 6, 1917, his voided urine was reported as follows: Gross appearance; amber; clear; flocculent sediment of mucus; albumin (cold nitric acid test) negative. Microscopic (centrifuged) fresh: moderate number of pus cells and mucus; stained; pus cells, very many tuberc'e bacilli in smaller and larger clumps.

Remarks. This patient has been under observation for five years —that is, since he first showed a tubercle bacilluria. Originally the inoculation tests from both kidneys were positive, though the slide examination was negative. As the patient had a distinct focus in his prostate and had no symptoms of persisting vesical

irritation, had brilliant clear urine, and normal kidney function, I was inclined to look upon the bilateral ureteral tubercle bacilluria as a contamination or as an excretory phenomenon. Others to whom I submitted the data in this case took Casper's attitude previously mentioned, and suspected a bilateral renal tuberculosis. After a period of quiescence lasting four years the original symptoms recurred, and by two cystoscopists practically the same data are found as at the earlier examination. Both kidneys functionate well; both ureteral specimens induce tuberculosis in the guinea-pig; but now the left kidney specimen contains more white cells than four years earlier and some tubercle bacilli are demonstrable in the smear from this side. Even now the bladder urine is brilliantly clear, though the sediment shows a moderate number of pus cells and tubercle bacilli. There is no frequency, no pain, and apparently the patient is in perfect health.

From all these data it is impossible to exclude a left renal tuberculosis. Such was my original suspicion five years ago. After careful study I felt convinced at that time that the kidneys were normal despite the positive inoculation tests on both sides, even though there were more leukocytes in the left specimen than is normal. What is the significance of the four positive inoculation tests with the right ureteral specimens? Has that always been due, both in the hands of others and of myself, to contaminations? Or is it an excretory bacilluria, derived from the prostatic focus? With such brilliant urine, without any vesical symptoms, with apparently perfect health and gaining weight, I believe I am not justified in recommending removal of the left kidney despite the fact that from this side we recovered nine months ago tubercle bacilli in the smear.

Case III (1003).—S., male, aged thirty-four years. Previous gonorrheal and syphilitic infection. Since the middle of 1915 swelling of left epididymis, associated with bladder irritability, terminal bleeding, and pain. These persisted for three months. An abscess formed in the left half of the scrotum and discharged pus. Gradually the swollen area diminished, but the sinus persisted.

June, 1916. This condition was still present. There was no vesical irritability. The patient was well nourished, and except for the discharging sinus leading to a tuberculous epididymis and an enlarged left prostatic lobe the patient was in excellent health. His urine was turbid and contained pus cells and tubercle bacilli.

June 23. Cystoscopy showed absolutely normal bladder. The lips of the left ureteral orifice appear slightly separated. After passing ureteral catheters some indigocarmine was introduced into the bladder, and it was recovered through the left ureteral catheter proving a definite reflux up this ureter. Subsequent argyrol and roentgen-rays, with bladder filled and patient in the Trendelenburg position, showed no ascent (really descent) up the ureters. The

left kidney shadow was normal in size. The bladder urine (by catheterization) showed a faint trace of albumin, many white and red blood cells, and many clumped tubercle bacilli. The left kidney specimen showed urea 0.2 per cent., a few white and red blood cells, and tubercle bacilli. The right kidney specimen showed: urea, 0.8 per cent., and epithelial cells and cylindroids. Guinea-pig inoculation from right side was negative.

June 24. Partial orchidectomy and epididymectomy (left side). After recovery from this operation the patient went to the country and gained almost twenty pounds. On his return in November he felt perfectly well, had no vesical symptoms and no tenderness in the lumbar region. In the left scrotum there was a narrow sinus and several, probably tuberculous, nodules. The voided urine was turbid while the catheterized bladder urine was much clearer. Both contained pus cells and tubercle bacilli. The bladder was thoroughly irrigated with 2500 c.c., and the terminal wash fluid was examined for tubercle bacilli, which could not be found in the smear but where demonstrable by the inoculation test, thus showing how difficult it is to wash the bladder clear of tubercle bacilli.

December 1. Cystoscopy shows a congested trigone. There is no evidence of disease in the bladder except a longitudinal area overlying the left vesicle to the outer side of the left ureteral orifice, where the mucous membrane is injected, edematous, and pushed forward by the underlying tuberculous left seminal vesicle. The right ureter admitted a catheter readily, and while the catheter was *in situ* 10 cm. up the ureter, an indigocarmine reflux up this ureter was demonstrable. The left ureter admitted a catheter 3.5 cm., and at this level it was obstructed. The catheterized bladder specimen showed a heavy sediment containing pus and epithelial cells. No red blood cells. Many tubercle bacilli. The specimen from the right kidney showed urea, 1.8 per cent.; no tubercle bacilli; a few red cells and epithelial cells. The specimen from the left kidney showed urea, 1.1 per cent.; very few tubercle bacilli; pus cells much less numerous than in bladder specimen; many epithelial cells, few red cells. The inoculation tests were positive on left side and both pigs used for the right side were negative.

February 5, 1917. Patient is in excellent condition. Has no frequency of urination and no pain.

Remarks. In this patient there is a definite left-sided genital tuberculosis, with pus and tubercle bacilli in his catheterized bladder urine. At the first cystoscopy a definite reflux up the left ureter was demonstrable, and the suspicion was entertained that this might account for the presence of the few tubercle bacilli and few pus cells as well as the apparently lower urea output on this side. Almost six months later, without the development of signs pointing to a definite renal involvement, a reëxamination was made, and now there was cystoscopic evidence of marked disease

of the left seminal vesicle, with obstruction to the passage of the ureteral catheter beyond 3.5 cm. Now there were more pus cells in the left kidney specimen than before. Does that mean left renal tuberculosis or does it point to a ureteritis of the lower end of this ureter, due to the marked inflammation of the adjacent seminal vesicle? Naturally a renal tuberculosis cannot be excluded. I am at a loss to interpret the significance of the ureteral tubercle bacilluria. It may owe its origin to any one or all three of the factors to which I have repeatedly called attention in this discussion.

In closing, I am in the unfortunate position that, despite careful study, I can make no categorical statements as to the significance of the ureteral tubercle bacilluria, and I come back to my opening remarks that each case must be decided upon its merits, and only after such careful study as each patient will permit may we be in a position to decide as to whether the tuberculous disease has involved the kidney or not. Before one has reached a definite decision that the ureteral tubercle bacilluria is due to renal tuberculosis, the next step, removal of the kidney, must be relegated to the future.

ALBUMINURIA AND HEMATURIA FOLLOWING THE ADMINISTRATION OF HEXAMETHYLENAMIN.

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Nicolaier, in 1894, was the first to note the fact that painful micturition and hematuria may at times result from the administration of hexamethylenamin even when given in small amounts. The occurrence of albuminuria and hematuria has been discussed from time to time, nevertheless the number of reported cases is not large and the subject has not received the attention it deserves. The following 5 cases are of interest:

Case I.—N. R., aged two years, during an attack of acute otitis media was given hexamethylenamin, gr. iiss, every four hours. No symptoms of urinary irritability were noted, but three days later the urine examination was as follows: Normal color; moderately turbid; contains a number of large shreds; acidity 110 degrees; 1023; albumin 0.25 per cent.; sugar and indican absent; aldehyde test negative. The microscope showed large numbers of blood and pus cells. The hexamethylenamin was discontinued, and six days later the urine had again become normal.

Case II.—Miss M., aged twenty-one years, was under treatment for neurasthenia and intestinal putrefaction. On August 6, 1913, the urine was bright green in color; moderately turbid; acidity 140 degrees; 1020; albumin and sugar absent; indican enormously

increased. The green color may possibly have been due to chemical changes in the large amount of indican which was present. The patient was ordered to take gr. x of hexamethylenamin three times daily. On August 11 she stated that for several days she had been troubled with severe pain and burning upon micturition, and on one occasion had noticed several small, flesh-like pieces in the urine. On that day the urine was very turbid; contained many large shreds; albumin ring very dense; indican moderately increased; the microscope showed many pus cells; squamous epithelium; uric acid and bacteria. After withdrawal of the hexamethylenamin the urinary irritability and the albumin disappeared.

Case III.—W. W., aged twenty-seven years, seen April 18, 1913. The patient had suffered repeated attacks of rheumatic fever and presented a chronic tonsillitis and a severe aortic and mitral endocarditis. The urine was of normal color; acidity 42 degrees; no albumin or sugar; indican moderately increased. He was ordered to take gr. xx of hexamethylenamin three times daily. When seen two days later he stated that about half an hour after the first dose of medicine he began to have burning urination. This increased in severity until the distress became very acute and the urine markedly bloody. Examination showed the urine to contain a large amount of blood; acidity 50 degrees; albumin a large trace. The hexamethylenamin was at once withdrawn, but the patient possibly may have decided to run no further risks, for he did not return for observation.

Case IV.—Miss W., aged eighteen years, seen March 10, 1912, presented signs of an infection of obscure origin, involving the urinary tract. March 12 urine examination was as follows: Very turbid; dirty yellow; acidity 110 degrees; 1025; slight trace of albumin; marked excess of indican; blood and pus cells frequent; squamous epithelium; urates and numerous bacteria. March 16 the albumin had disappeared. A prescription containing gr. v of sodium benzoate and gr. x of hexamethylenamin was given, to be taken three times daily. March 19 the urine showed a large amount of albumin, estimated at $\frac{1}{5}$ per cent., and an increased amount of blood. Five days later, March 24 the albumin had increased to 0.5 per cent., Esbach. The patient complained of some pain and burning on passing urine. The hexamethylenamin was withdrawn, and eleven days later, May 4 the albumin had entirely disappeared. A few days afterward the hexamethylenamin prescription was again started, but on May 17 the urine presented a large amount of albumin, estimated at 0.25 to 0.5 per cent. When the hexamethylenamin was a second time withdrawn the albumin promptly subsided to the usual slight trace. The signs of urinary infection continued for over a year, and June 13, 1913, helmitol, a citric acid salt of hexamethylenamin was prescribed in doses of gr. v, t. i. d. The urine on that day showed only the slightest possible trace of albumin.

No symptoms of urinary irritation were noted, and three days later the dose was increased to gr. x three times daily. June 15 five days after the administration of helmitol had been begun, the urine showed 0.25 per cent. of albumin, with considerable blood and pus. The helmitol was promptly discontinued and the urine again returned to its usual condition, showing only the slightest possible trace of albumin June 23.

Systematic investigation of the urinary tract proved the infection to be limited to the bladder. Bacteriological examination of the urine showed the Bacillus coli communis, together with other unidentified forms. Several examinations of the catheterized urine failed to reveal tubercle bacilli, and guinea-pig inoculation was negative for tuberculosis.

Case V.—Miss F., aged thirty-five years, consulted me June 26, 1915, for a subacute cystitis. She was treated by bladder irrigations with silver nitrate solution. Because of the alkaline reaction of the urine, acid sodium phosphate was given in addition to hexamethylenamin. On two occasions symptoms of urinary irritability appeared, together with slight albuminuria. In each instance the urinary acidity was very high, 70 and 110 degrees respectively. After a brief withdrawal of both drugs the disagreeable symptoms promptly disappeared.

Less than a decade ago, Crowe and others showed that after the ingestion of hexamethylenamin the drug could be demonstrated in practically every fluid of the body. These investigations led to the hope that we were in possession of a therapeutic weapon which would prove to be of great efficiency in many infectious diseases. Practising physicians began to use hexamethylenamin in a wide variety of infections (many still continue to employ it), expecting it to present the same striking benefits already observed in certain urinary disorders. The results have usually proved disappointing, and further laboratory studies have already shown the reasons for failure.

The therapeutic effects of hexamethylenamin depend entirely upon its conversion into ammonia and formaldehyde. Hexamethylenamin itself has no antiseptic action, even in as strong a concentration as 10 per cent., and the only object in giving the drug is to administer weak formaldehyde. The liberation of formaldehyde may possibly occur to a slight extent in neutral or weakly alkaline solutions, particularly if exposure to the action of the drug continues for considerable time, but for practical purposes no formaldehyde is formed save in an acid medium. Urine, gastric juice, and sweat are the only acid secretions of the body, and the therapeutic action of hexamethylenamin must therefore be limited to these secretions. Not only has hexamethylenamin been found in practically all normal body fluids, but likewise in various pathological exudates, such as serous effusions, pus accumulations, discharge

from otitis media, etc.; yet competent investigators have been unable to demonstrate the presence of formaldehyde in any of these fluids.

The liberation of formaldehyde from hexamethylenamin depends upon three factors: the concentration of the drug, the duration of its action, and the acidity of the medium. These facts have practically limited its therapeutic application to diseases of the urinary tract, principally those of the bladder, although further study may show it to be of service in stomach diseases or in certain skin disorders accompanied by acid sweat.

The longer the urine is retained in the bladder and the higher its acidity the greater will be the formaldehyde production. Degrees of acidity less than 20, expressed in terms of decinormal sodium hydrate, are not favorable. In strongly alkaline urine the drug is useless, but in such a condition acid sodium phosphate (not the sodium phosphate commonly used) may be administered to render the urine acid. To give hexamethylenamin in combination with an alkali is entirely irrational.

Clinically the best results of hexamethylenamin medication are seen in the urinary bladder. Here we have an acid medium, a favorable temperature, and an exposure of the urine to the action of the drug for a variable period, often several hours. It is believed that hexamethylenamin is not broken up into formaldehyde and ammonia until it reaches the bladder. This would explain its disappointing action in many cases of pyelitis and other kidney diseases. In certain individuals, particularly if the urine presents a high degree of acidity, it is possible that formaldehyde conversion may occur in the kidney itself. Even in these cases, however, the urine is passed along into the bladder so rapidly that any therapeutic action is questionable. The possibility of renal irritation from the formaldehyde, which perhaps is occasionally split off in the kidney, must be kept in mind. Under ordinary conditions, however, hexamethylenamin causes no irritation of the kidneys.

When untoward effects appear during the course of hexamethylenamin administration they usually may be traced to the following causes: Insufficient dilution of the drug, high urinary acidity, or personal idiosyncrasy. The most common symptoms are those of vesical irritability, and may vary from slightly increased frequency of micturition to severe vesical tenesmus or even strangury. Albumin or blood is often present in the urine. Unless obscured by blood the macroscopic appearance of the urine is very characteristic. It is pale in color, turbid from pus cells, and shows a large number of flakes and shreds which are different than those seen in any other condition. The source of the blood found in patients showing urinary irritation is probably the bladder. Crowe reports that in dogs in whom an experimental hematuria had been produced by enormous doses, after the subsidence of acute symptoms, microscopic

examination of the kidneys failed to disclose any evidence of permanent damage. Of 95 patients who had received an average daily dose of 75 grains for ten days, painful micturition and hematuria occurred seven times. In 3 of the cases which came to autopsy it was apparent that the hematuria had its origin from the mucous membrane of the bladder and was not due to acute renal irritation. In the remaining 4 cases the urine rapidly became normal upon the withdrawal of the drug.

The source of the albumin found in similar cases has not been conclusively demonstrated. Levy and Strauss believe that individuals with a high urinary acidity may liberate formaldehyde in the kidneys, and under these conditions may develop hematuria or albuminuria. In the writer's cases no renal elements were found in any of the specimens of urine examined, yet the large amount of albumin present in some instances pointed to a kidney rather than a bladder origin.

The treatment of irritation of the urinary tract following the administration of hexamethylenamin is simple. Withdraw the drug, give large amounts of fluid, together with alkalies, and in a short time conditions will almost invariably return to normal. If hexamethylenamin were always prescribed with large quantities of fluid, many, although not all, cases of irritation would be avoided.

In the treatment of pyelitis and other kidney conditions, results cannot ordinarily be obtained unless large doses are given and the urine is highy acid or is rendered so, preferably by acid sodium phosphate. Such patients must be carefully watched for signs of urinary irritation.

A study of the writer's cases leads to the conclusion that the most important cause of albuminuria or hematuria following the administration of hexamethylenamin is abnormally high urinary acidity. In 4 out of the 5 reported cases the acidity was above 100 in terms of decinormal sodium hydrate, and in Case II, it reached the exceedingly high figure of 140. It is therefore necessary to carefully determine the urinary acidity of all patients who are taking hexamethylenamin. If the acidity becomes too low or disappears entirely the drug is inefficient, whereas with a high degree of acidity, irritative symptoms are likely to appear. High dilution of the urine impairs the formaldehyde action; concentratration of the urine increases formaldehyde activity, but favors unpleasant results. The physician must therefore steer a middle course.

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TUBERCULOUS PERITONITIS.

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Tuberculous peritonitis is a condition that occurs much more frequently than is recognized, because, (1) it occurs in a latent form without symptoms and is discovered only at autopsy or during laparotomy for other conditions, and (2) its manifestations are so varied that the diagnosis is often obscure. This is true particularly of the localized forms. The history of many cases of tuberculosis of the peritoneum is that of recurrent attacks of abdominal symptoms with intervals of freedom from the symptoms. It is only when the process becomes extensive enough or gives sufficient evidence on examination to warrant a diagnosis that the condition is recognized. Many of these, in view of the tendency to spontaneous recovery, never reach this stage, and the disease becomes limited before recognized or even suspected. The cases that are diagnosed, therefore, are usually advanced cases. Tuberculous peritonitis may occur at all ages, but its occurrence is noted more frequently between twenty and thirty years of age. It is usually associated with tuberculosis of other portions of the body, and primary tuberculous peritonitis is rare, if it ever occurs. The frequent association of tuberculous peritonitis with genital tuberculosis in both sexes,

pulmonary tuberculosis, tuberculous adenitis, or tuberculosis of some portion of the intestinal tract is an aid to its diagnosis, and in the presence of these forms of tuberculosis any abdominal symptoms or complications should suggest the possibility of tuberculous peritonitis. The coexistence of involvement of another serous cavity, especially the pleural cavity, is of great importance in diagnosis. In women it is frequently associated with underdevelopment of the genital organs and sterility. The occurrence of tuberculous peritonitis as a part of a general miliary tuberculosis will not be considered here. The disease occurs in three forms: the miliary, 68 per cent., the chronic adhesive, 27 per cent.; the chronic ulcerative, 4 per cent. Symptomatically we have the acute, the subacute, and the chronic types, the latter two usually merging into each other. The acute type may simulate acute appendicitis or intestinal strangulation, and the temperature may reach 103° and 104°. The subacute type with abdominal pain and tenderness, continued fever, distention, diarrhea, and relatively low leukocyte count may be confused with typhoid fever. In the subacute and chronic types the presence of fluid or tumor masses usually leads to the diagnosis, especially when there are multiple masses present. We have found that the presence of palpable nodules due to conglomerate tubercles on the peritoneum of the cul-de-sac, which are readily felt on rectal examination, has been of value in diagnosis, although in these cases metastatic new growths must be ruled out. In 4 of our cases these nodules were felt on rectal examination. Moderate distention, abdominal tenderness without muscle spasm, abdominal discomfort, anorexia, alternating constipation and diarrhea, irritability of the bladder, weakness, loss of weight, and sometimes vomiting may be prominent features; in fact, the symptoms are most varied, and this disease may simulate almost any intra-abdominal condition, as is evident by the variety of incorrect diagnoses made in this disease. The symptoms and signs due to the presence of excess of fluid may constitute the whole clinical picture. Pigmentation of the skin occurs in quite a percentage of the cases, and there is usually a rise of temperature which varies from a high continued fever to a slight evening elevation. Normal or even subnormal temperature may be present. Blood-pressure is usually low. A normal or slightly increased leukocyte count with relative lymphocytosis is usually present as in other forms of tuberculosis, and is a diagnostic aid.

The tuberculin tests are o limited value. We have had some interesting experiences with the von Pirquet test, in that in several of the cases a weakly positive test became strongly positive as the patient's condition improved, especially in the rapid improvement that sometimes follows a laparotomy. In one instance a negative von Pirquet test on admission of the patient made us doubt the presence of a tuberculous process. This patient was emaciated

and anemic, and there were multiple masses felt in the abdomen and on rectal examination nodular masses were felt in the cul-de-sac. The negative von Pirquet test made the diagnosis of malignancy very probable, although our first impression was that of tuberculosis. After several weeks of treatment, in which the patient's general condition improved, the von Pirquet test was repeated and found positive. This was absolutely diagnostic, and at operation extensive tuberculous involvement was found. This patient was evidently so overwhelmed with the infection when first observed that there was no reaction to tuberculin; but as improvement took place and the patient attained a resistance there was again a response to the tuberculin test. We have seen several very weakly positive von Pirquet tests in tuberculous peritonitis, and in three the test was absolutely negative The subcutaneous test is of value in the afebrile cases, but should be used with caution. When there is ascites it is sometimes difficult to differentiate from cirrhosis of the liver, especially since the two are often associated, the cirrhosis with ascites apparently predisposing to tuberculous infection of the peritoneum. The cytology and bacteriology of the fluid is not of much value in differentiating from other types of ascites, because tapping of the abdomen is dangerous in this condition, as the ascitic and adhesive processes are frequently combined and the danger of puncturing the intestine is a real danger. Tubercle bacilli are seldom found in the fluid. A lymphocytosis of the fluid is suggestive of tuberculosis, as is also the presence of a bloody fluid. The fluid is usually straw-colored or bloody, and may be purulent in the chronic ulcerative form. Encysted fluid in the midline, often mistaken for an ovarian cyst, and tumor due to rolled-up omentum lying transversely across the upper abdomen are frequently observed in the chronic forms. Multiple irregular masses often lead to the diagnosis of a malignant condition. It is interesting to note that in 2 of our cases the appendix had been removed previously, with diagnosis of chronic appendicitis, but without relief of symptoms.

The prognosis of tuberculous peritonitis is good. Oschner states that 50 per cent. are cured by medical treatment alone and that 50 per cent. of the remainder are cured by surgical intervention. Cases should be well for at least three years before pronounced cured, as there are many relapses within that time. The prognosis is affected unfavorably by the presence of active tuberculosis of the lungs or extensive intestinal tuberculosis. Persistent diarrhea usually signifies intestinal involvement.

Of the different forms of tuberculous peritonitis the chronic ulcerative caseating variety presents the least chance of recovery with either method of treatment. Collections of pus in the abdominal cavity or between coils of intestines, perforation, and fecal fistulæ are to be feared in this variety.

The history of tuberculous peritonitis is that it was at one time considered hopeless. This was followed by the surgical age in which all cases were operated, with a high percentage of reported cures, which, however, failed to stand the test of time. The pendulum swung back to where operation was considered by some as of no benefit, while others insisted on its value. Today there is an effort to select those cases which are best suited for so-called medical treatment and those in which surgical procedures are indicated. There is no doubt that in properly selected cases, laparotomy, under conditions which throw the least strain on the reserve strength of the patient, is followed by a much more rapid and marked primary improvement in the condition than under medical treatment alone, and that in cases that are apparently at a standstill or in which the process is actually extending, laparotomy frequently turns the tide and is followed by improvement. The medical treatment is always indicated, and operation should be merely an incident in the general plan of treatment. In patients who were not considered proper subjects for surgical treatment when first seen, and were treated medically until conditions were more favorable, we have repeatedly observed that the comparatively slow improvement under medical treatment was followed by rapid improvement after laparotomy, and that surgery deserves a place in the treatment of tuberculous peritonitis cannot be denied. The objection that the cures are not permanent and that recurrences occur is just as true of medical treatment. In properly selected cases the primary improvement is usually marked, but these patients must be kept under a careful régime until the danger of recurrence is past.

The treatment of tuberculous peritonitis should be similar to the treatment of tuberculosis elsewhere, in that it should be primarily the treatment of the patient's general condition and the treatment of the local condition is secondary, since complete surgical extirpation of the diseased area is impossible. There have been various theories as to the way in which simple laparotomy acts favorably in these cases. The most logical one seems to be that the good effects of laparotomy come from the resultant hyperemia from exposure of the peritoneum to the air. Nassauer reopened the abdomen three hours after operation for tuberculous peritonitis and observed a hyperemia of a degree which he says cannot be appreciated unless actually seen. Laparotomy in experimentally induced tuberculous peritonitis in rabbits is followed by a hyperemia of greater degree and longer duration than in rabbits without tuberculous peritonitis. This is due to the action of air on the peritoneum as it does not occur if the operation is done with the animal submerged in normal salt solution. It is this hyperemia that we aim to get in the use of tuberculin in the focal reaction. It is the foundation of Bier's hyperemia treatment of tuberculosis. Tuberculous lesions anywhere in the body are healed by encapsulation

with fibrous tissue. The lymphocytes play a part in the fight against tuberculosis analogous to the part played by the leukocytes in other infections. There is a zone of lymphocytes surrounding the tubercle and a relative lymphocytosis in the blood just as there is a zone of polymorphonuclear leukocytes around a pyogenic infection and a polymorphonuclear leukocytosis in the blood. In this hyperemia more blood and more lymphocytes are brought to a relatively chronic lesion, and in this way the natural processes of combating the tubercle bacilli and encapsulating them with fibrous tissue are aided. There is also an absorption of the products of growth of the tubercle bacilli as a result of this hyperemia which is equivalent to a dose of tuberculin. This is greatest in the acute cases and becomes less in the more chronic types. It is because of their absorption that laparotomy in the acute types may be actually harmful. That such absorption takes place is well shown in Case No, 15 of our series, in which the temperature rose sharply to 105° following simple laparotomy. This is equivalent to a large dose of tuberculin, and therefore is contra-indicated in the acute types of the disease in which the patient is already absorbing more than he can properly care for. For this reason patients with continuous fever above 99.5° or 100° should be treated conservatively until the process becomes more chronic. We hesitate to operate upon these cases for the same reason that we hesitate to give tuberculin to patients when the temperature is elevated. It is a different proposition from that in which a tuberculous lesion can be completely excised.

The best results surgically are obtained in the chronic types with little or no fever, and especially in the miliary form with ascites. The impression that the fibro-adhesive form is not amenable to surgical treatment has not been our experience, for the types so frequently overlap, the miliary form being present in one portion of the abdomen and the fibro-adhesive form in another, the one form apparently an advanced stage of the other, and a complete disappearance of both may occur after laparotomy.

Because of this overlapping of forms, on opening the abdomen if we encounter adhesions we lengthen the incision in an effort to get into the free peritoneal cavity, where we may find the miliary form. The operative procedure should be as simple as possible, consisting of laparotomy, with evacuation of fluid, if present, exposure of the peritoneum to the air, with a minimum of trauma and intra-abdominal manipulation, and closure of the incision without drainage. Intra-abdominal medication is useless. Extensive breaking up of adhesions and the use of drains predispose to fecal fistulæ and persistent sinuses, usually from secondary infection. The chronic adhesive form of tuberculous peritonitis is a healing process, and to break up these adhesions, unless for the purpose of relieving intestinal obstruction, is meddlesome surgery. The focus of infection should be removed only when it can be done with little manip-

ulation. The operative treatment is largely a local treatment and the patient should be in as good general condition as possible, and the operation should not be so severe as to tax the patient's resistance. It should be done under conditions that conserve to the greatest degree the strength of the patient, preferably under local or spinal anesthesia, preceded by the use of opiates.

The conservative or non-operative or so-called medical treatment with which the surgical treatment should always be combined consists of keeping the patient at rest in bed and outdoors and on as liberal a diet as possible. When the temperature comes down we give tuberculin, estimating the dose for each individual patient by the method that was developed at the Tuberculosis League in Pittsburgh. During the last two years we have been following Rollier's method of heliotherapy with good results. Although conditions in Pittsburgh are not as favorable for this form of treatment as are those in Switzerland, we feel that our results have been better since instituting this plan. Limited portions of the body are exposed daily for short periods to the direct rays of the sun, gradually increasing the surface and the time of exposure until the whole exposed body is well tanned. The head should be protected and the eyes shielded from the glare of the sun, and care should be exerted as to the rapidity in which the exposures are increased, judging this chiefly by the way the patient responds. Headaches and exhaustion are indications of improper reactions. The process of tanning should be gradual and sunburns should be avoided. By keeping the patient in the sun covered only by a sheet the tanning process takes place to a certain extent at times other than when the parts are directly exposed. These patients should be treated until all signs and symptoms of the disease have disappeared, and a similar régime should be followed as nearly as possible for at least six months after the patient is allowed to walk. The patient should be observed for at least three years, for the brilliant results of any treatment are much dimmed by the large percentage of cases that fail to stand the three-year test that is insisted upon as essential to a cure. The prognosis of localized tuberculosis in children under conservative treatment is always better than in adults, and the indications for operation are less in this as in other forms of surgical tuberculosis in these young patients. We have had no experience with the roentgen-ray treatment of this disease.

This paper is based on the analysis of 21 cases. Two left the hospital without operation, and in 1 case that died no autopsy was obtained. In the remaining 18 the clinical diagnosis was confirmed at operation or autopsy.

Treatment and Results. Of the 21 cases, 14 were operated on at the St. Francis Hospital and 2 had been operated elsewhere; 5 were not operated. Of the 5 cases that were not operated, 3 died in the hospital, 2 of them within two days after admission, and the

other 1 in two and a half weeks. One case refused operation and left the hospital in three weeks unimproved. The other case was of the acute type and simulated typhoid fever. This patient was not considered as the type for operation, and was treated conservatively and left the hospital improved. Of the 2 cases operated on at other hospitals and admitted later to the St. Francis Hospital, 1 left improved and the other unimproved. This patient refused to remain longer than three weeks. Of the 14 cases operated on at the St. Francis Hospital 1 died ten weeks after operation. This patient had tuberculous pleurisy and the chronic adhesive type of tuberculous peritonitis. The von Pirquet reaction was negative. Adhesions were so dense that a very limited portion of the abdomen was exposed. The patient became greatly emaciated before death. The differential count in this case one week before operation showed 3.7 per cent. small mononuclears. We believe that this is important and that a low lymphocyte count indicates a low resistance. The remaining 13 cases were discharged improved, with temperature normal or with only an occasional rise in the evening, and a diminution in size or a disappearance of palpable masses and with no evidence of reaccumulation of fluid, and with an improvement in the patient's general condition. In 3 of these cases differential counts were made before and after operation, and all of them showed a marked increase in lymphocytes after improvement. Most of the cases showed a marked primary improvement soon after operation. The average duration of treatment in the hospital before operation was two weeks and after operation eight and a half weeks. One case had been treated for five weeks at the St. Francis Hospital five months beforehand with diagnosis of typhoid fever (?). On second admission diagnosis of tuberculous peritonitis was made and confirmed at operation. Another case simulated typhoid fever until the clinical diagnosis of tuberculous peritonitis was made by finding nodules on the peritoneum of the cul-de-sac. The fluid from the peritoneal cavity was examined in 2 cases, the one showing a specific gravity of 1022, and contained 91 per cent. lymphocytes. The other one showed 69 per cent. lymphocytes. No tubercule bacilli could be demonstrated in smears or on injection of guinea-pig.

End Results. Letters were sent to 17 patients. Three of the letters were returned unopened. No replies were received in 8. Five reported as well. One of these was operated six years ago and one three years ago. The remaining 3 were operated on in the last two years. One of the cases, not operated, reported as improved, but has occasional attacks of abdominal discomfort.

Analysis of Cases. The oldest patient was sixty-three and the youngest two years of age. Eleven were between twenty and thirty years. There were 11 females and 10 males. There was 1 case of the chronic ulcerative type, 5 of the chronic adhesive, and the remainder the miliary with or without fluid and adhesions. In

4 of this series there is a note of palpable nodules in cul de sac. Six patients were recorded as well nourished. The rest were poorly nourished or emaciated. In 17 of the cases there is record of one or more leukocyte counts. The highest count was 16,000. This was in the 1 case of the chronic ulcerative type with pus formation. The lowest count was 5150. This patient died without operation. No differential count was made. Average white cell count in the series was 9990. The hemoglobin was recorded in 15 cases, the highest being 90 per cent., the lowest 52 per cent., and the average 72 per cent. Differential counts were recorded in 11 cases, with an average of 28.3 per cent. mononuclears. There was a differential count on only one of the fatal cases. This patient died ten weeks after operation, and was the only operative fatality. The count was made one week before operation, and showed 3.7 per cent. small mononuclears and 14.9 large mononuclears. Differential counts before and after operation were recorded in only 3 cases. In 1 there were 9 per cent. small mononuclears and 11.5 per cent of large mononuclears three weeks before operation, while two and a half months after operation there were 27 per cent. of small mononuclears and 5 per cent. of large. In another there were $17\frac{1}{2}$ per cent. of small and and $7\frac{1}{2}$ per cent. of large mononuclears two days before operation, and one month after operation there were 33 per cent. of small, and 5 per cent. of large mononuclears. In the other case seven days before operation there were 20 per cent. of small mononuclears and 10 per cent. of large, while thirteen days after operation the small mononuclears were 30 per cent. The von Pirquet test was done in 9 cases. Six were positive and 3 were negative. One of these became positive later. The Wassermann test was done in 3 cases and was negative in all of them. There were no cases of primary tuberculous peritonitis, for other organs were found involved in all of the cases, namely:

Glands in 8; adnexa and lung in 1; lungs in 3; lungs and testicle in 1; lungs and pleura in 3; pleura in 3; meninges in 1. Of the 6 cases with pleural involvement, 4 had effusion.

In 9 of the 14 patients no organs were removed at operation. In the remainder the tubes or the appendix were removed. Drainage was used in 2 cases. In one of these, the ulcerative type, a fecal fistula followed. In the 2 patients operated elsewhere there were sinuses, but it is not known whether drainage was used. In 3 of the cases in which no drainage was used a sinus appeared later and persisted for a variable length of time.

REVIEWS

EYE, EAR, NOSE AND THROAT. By HOWARD CHARLES BALLENGER, M.D., Professor of Oto-Laryngology in the Chicago Eye, Ear, Nose and Throat College, etc., and A. G. WIPPERN, M.D., Attending Oculist and Aurist to St. Elizabeth's Hospital, Chicago, etc. New second edition, thoroughly revised. Pp. 524. Illustrated with 180 engravings and 8 colored plates. Philadelphia and New York: Lea & Febiger, 1917

THIS little text-book on the eye, ear, nose and throat, written by authors whose names in themselves are a guarantee of excellency, now appears in its second edition. It is a small concise work written for the use of students and general practitioners. In this edition there has been a radical revision of the greater part of the book; enlarging and improving the chapters on anatomy and methods of examining the ear and adding chapters on malformations of the external nose and the technic for tonsillectomy. The book is well balanced, covering the whole field of the eye, ear, nose and throat and giving sufficient detail concerning the more common diseases and operations for a fairly comprehensive knowledge of the matter. We regret, however, that more space has not been given to the section on the ear, and especially to the modern method of examining the static labyrinth and its relation to cerebellar disease. Also the pathology is disappointing, being frequently not mentioned and generally unreliable. As a practical treatise, however, we heartily recommend this book as a useful addition to the general practitioner's library, and the descriptions of the technic more of the common operations will be a great help to the beginner in this specialty. The illustrations are above the usual, and there is appended a formulary for the ear, nose and throat.

G. B. W.

MODERN MEDICINE AND SOME MODERN REMEDIES. PRACTICAL NOTES FOR THE GENERAL PRACTITIONER. By THOMAS BODLEY SCOTT. First edition. Pp. 159. New York: Paul B. Hoeber.

THE book consists of four essays upon the following subjects: disorders of the heart, arteriosclerosis, therapeutic speculations, and

doubts, and chronic bronchitis and bronchial asthma. It is of special interest, as it is a publication of facts as observed by a general practitioner. It also sets forth the difficulties of a general practitioner in handling heart and arteriosclerotic cases.

In speaking of valvular disease as results of an infection process, there is a failure to mention tonsillitis and chorea as important etiological factors. Syphilis, especially in America, plays a greater role in the etiology of aortic valvular disease than the author brings forth.

The presclerotic period is well exemplified by the author as well as the important use of the sphygmomanometer and the simple management of these cases.

The results of internal secretion medication are well drawn and practical. The use of autogenous vaccines, grown anaërobically, in bronchial asthma, with their results is well shown and there is no doubt of their good effect in riding the patient of his severe bronchitis after which the asthma apparently clears up.

The book is well written and should serve its purpose in stimulating other general practitioners to tabulate and hand down many useful points observed at the bedside. T. K.

PRINCIPLES OF DIAGNOSIS AND TREATMENT IN HEART AFFECTIONS. By SIR JAMES MACKENZIE, M.D., F.R.S., F.R.C.P., LL.D. Ab. and Ed., F.R.C.P.I. (Hon.), Physician to the London Hospital (in charge of the Cardiac Department), Consulting Physician to the Victoria Hospital, Burnley. Pp. 264. London: Henry Frowde, Oxford University Press. Hodder & Stoughton, Warwick Square, E. C.

THIS book contains a series of lectures which were to have been delivered to the postgraduate students and workers at the Cardiac Department of the London Hospital. The outbreak of the war having prevented their delivery the author presents them in book form.

The purpose of the lectures is not only to give the essential features concerning heart failure in a manner useful to the practitioner, but also to offer a better insight into clinical medicine and thus stimulate research in this line. In regard to the evidences produced by mechanical aids, as the polygraph and electrocardiograph, the reader is referred to the author's book on *Diseases of the Heart*.

The first chapter deals with the subject of medical research and shows how the progress of medicine has been and will be delayed until the practitioner becomes more of an investigator. The value

of close observation and carefully kept records the author supports as the essential features for the foundation of clinical research. Further emphasis is laid upon the recognition and significance of the patient's sensations in order to establish an early diagnosis and satisfactory treatment.

The author next discusses heart failure along practical lines, mentioning the functional properties of the heart muscle, its action in rest and in activity, exhaustion of reserve force, and early subjective sensations, etc. The patient's sensations and the production of symptoms are next considered, the chapters on breathlessness, syncope, and objective signs of heart failure containing much of use to the physician, who, after some practical experience, wishes to review the subject. The chapter on angina pectoris, viewed as an expression of exhaustion of the heart muscle, gives a basis for sound prognosis and rational treatment. Such terms as "pseudo-angina," or "mock angina," the author suggests are merely used to "cloak our ignorance by a vain and empiric nomenclature."

The true significance of murmurs—physiological, functional, and organic—is very clearly presented and the observations and conclusions based on many years of experience cannot fail to be of material use to the general practitioner. Just how frequently these murmurs are misunderstood is revealed by numerous instances cited by the author. Under heart irregularities he offers a good classification into the "youthful" and "adult" types, and again calls attention to the failure of the practitioner to grasp the real significance of these irregularities.

He speaks of the "doctrine of back pressure, with its attendant verbiage of compensation and decompensation," as having "blinded the profession to the real facts for the past sixty years," and shows how a clear understanding of auricular fibrillation furnishes a true knowledge of what heart failure really means. His chapter on blood-pressure is a conservative one and sounds a wholesome warning in regard to the too free offering of an opinion based on blood-pressure readings alone. Many useful suggestions are given under prognosis and treatment; and while the latter might not be considered by some as being particularly comprehensive, it is, above all, practical and sound.

The author's views are refreshing in regard to the much flaunted Nauheim baths, the reputation of which, he concludes, rests more on "brazen advertisements, financial interests, and slavish tributes of other spas than on an intelligent appreciation and application of the principles of therapeutics."

The usefulness of the book may be appreciated when one considers its foundation, which is based on many years of close observation and careful study, in which recent advances find their place and to which personal views are freely contributed. A. H. H.

VENESECTION: A BRIEF SUMMARY OF THE PRACTICAL VALUE OF VENESECTION IN DISEASE. By WALTER FOREST DUTTON, M.D. First edition. Pp. 220; 3 full-page plates. Philadelphia: F. A. Davis Company.

A BRIEF, yet a complete, review of the history of blood-letting from earliest Egyptian restrictions of surgical procedure, 2500 B.C. until the present time. The evolution from the crude methods of that time, through the different European periods, as advocated by the fathers of medicine as Hippocrates, Galen, Belsur and others. It is told in a most interesting and helpful manner.

The chapter on hematology is a text-book description and prepares the way for a brief and concise discussion of the etiological and therapeutic benefits of venesection. It is arranged systematically, with indications, technic and results to be obtained.

The author still advises cutting down on the vein. I have found it more practical, quicker, and less disagreeable to the patient to use a No. 18 needle to which is attached a three way stop cock. To one of the ways a tube leading to a vacuum bottle, as in an aspirating outfit. To the other way a sterile funnel is attached, so that in toxic conditions normal saline can be introduced if desired. I have had no trouble in securing 20 to 30 ounces of blood and in less time than by "breathing the vein."

The chapters upon heart diseases and hypertonia vasorum cerebri are especially well taken. The author quotes frequently most of the authorities, and all the material is especially well chosen. Many of the vague symptoms are explained on a substantial pathological basis. The book is most helpful to a busy practitioner. T. K.

CLINICAL DISORDERS OF THE HEART BEAT: A HAND-BOOK FOR PRACTITIONERS AND STUDENTS. By THOMAS LEWIS, M.D., D.Sc., F.R.C.P., Assistant Physician, University Hospital College. Third edition. Pp. 116; 54 illustrations. New York: Paul B. Hoeber.

A REPETITION of the two previous editions, with the addition of eleven pages to the chapter on auricular flutter, also alterations and changes in diagnosis. The book gives a clear cut and concise description of the important cardiac irregularities recognizable without the aid of the polygraph or the electrocardiograph. It is invaluable to the student who wishes to understand cardiac irregularities from the modern conceptions. The simplicity in which it is written is a valuable asset. The chapters upon heart-block and auricular flutter are of special interest. T. K.

SURGICAL NURSING AND TECHNIC. By CHARLES P. CHILDE, B.A., F.R.C.S., Eng., Lieut.-Colonel, Royal Army Medical Corps (Territorial); Senior Surgeon, Royal Portsmouth Hospital; Medical Officer in charge of the Surgical Division, 5th Southern General Hospital, Portsmouth. Pp. 229, 9 plates. New York: William Wood & Co.

THE title of this small treatise has been changed in issuing it in a second edition. The general make-up, however, remains the same, except for many changes brought about by the military aspect of English nursing since the onset of the war. The author takes up antisepsis and asepsis briefly, follows this by three excellent chapters on the care of the patient before, during, and after operation from the stand-point of the nurse. There is a chapter devoted to the selection of instruments and one upon operations in private houses. The final chapter is devoted to a discussion of nursing in military hospitals. A rather interesting feature of the book is the way the author takes up the cudgels for the betterment of the economic conditions of the nurse in training. The volume is an interesting book for the surgical nurse. P. F. W.

PREVENTIVE MEDICINE AND HYGIENE. By MILTON J. ROSENAU, Professor of Preventive Medicine and Hygiene, Harvard; Director of the School for Health Officers of Harvard University and Massachusetts Institute of Technology; formerly Director of the Hygienic Laboratory, U. S. Public Health Service, etc. Second edition. Pp. 1286; 172 illustrations. New York and London: D. Appleton & Co.

SUCH an exhaustive treatise as this one from Dr. Rosenau is baffling to review. Each subdivision is an epitome of the best and most modern scientific though upon the subject treated, and carries with it the authoritativeness that can come only from those of such large experience as the author and his colaborators. This review consequently attempts merely to indicate the wide extent of the work and to recommend it to all those interested in any branch of the subject.

As was stated in the preface to the first edition, "the work is planned to include those field of the medical and related sciences which form the foundation of public-health work," and it is the only American book covering this wide range. The first section deals with the prevention of the communicable diseases, and the author's presentation of this subject is unique in that the diseases are taken up in accordance with their mode of transference, as is suggested, for instance, by such chapter headings as "diseases having specific

or special prophylactic measures," "diseases spread largely through the alvine discharges," "insect-borne diseases," etc. In this way, from the preventionist's view-point, the emphysis is placed where it belongs.

The second section deals with immunity, heredity, and eugenics in a very comprehensive and enlightening manner. Foods, air, soil, and water respectively are discussed in the following divisions. The sections upon sewage and refuse disposal are presented by George C. Whipple, and are sufficiently detailed to be of invaluable aid to those engaged in such sanitary problems. Vital statistics is covered by John W. Trask. The division devoted to industrial hygiene and diseases of occupation is a satisfactory, but very limited, presentation of that very interesting group of disease conditions and of the known means of preventing them. Other parts of the work deal with schools, disinfection, and military hygiene.

Among the subjects which are new to this edition are the Schick reaction, the Bang method of suppressing bovine tuberculosis, emetin, certain insecticidal agents, standardization of bacterial vaccines, sodium fluoride, hydrofluoric acid, carbon dioxide in alveolar air, sanitary significance of odors, etc. T. G. M.

THE PRACTICE OF UROLOGY. A SURGICAL TREATISE ON GENITO-URINARY DISEASES, INCLUDING SYPHILIS. By CHARLES H. CHETWOOD, M.D., LL.D., F.A.C.S., Professor of Genito-urinary Surgery, New York Polyclinic. Second edition. Pp. 825; 325 illustrations. New York: William Wood & Co.

THE second edition of Chetwood's *urology*, appearing in three years after the first, deserves and will undoubtedly be received with the favor which characterized its predecessor. The frontispiece, a collection of fifteen figures from a cinematograph film depicting nephrolithotomy and nephrectomy, is a popular creation of the hour, but it is doubtful if much real surgery will ever be taught by the spectacular method of moving pictures. As we had occasion to remark previously, the attention given by the author to bacterin, or "vaccine," therapy in the chapter on serodiagnosis and serotherapy is especially commendable, although we would take exception to any description or recommendation conducive to a popularization of "phylacogens." Criticism might be offered that it would be advisable to include the working technic of the complement-fixation tests for syphilis and gonorrhea.

The chapters are well proportioned and noteworthy in the new edition, are innovations relative to the teaching of cystoscopy, also the additions of practical advantage in the operative technic and the new section on local anesthesia. More attention has been given to the technic of administration of salvarsan and neosalvarsan.

In the chapter on functional renal diagnosis the author's preference for the phenolsulphonephthalein test and the estimation of urea volume of the urine is noted. We cannot agree that the indigocarmin test is "less accurate," and contend that even though only 25 per cent. of the amount injected is eliminated by the kidneys, that this offers no disadvantage to its practicability and reliability. Exception must also be taken to the author's technic of employment of this test. Insufficient attention is accorded the renal tests of retention, especially total non-protein nitrogen and the blood-urea nitrogen.

The final 107 pages are devoted to a consideration of syphilis, and the subject is extremely well covered in this space. Some of the illustrations, particularly the borrowed ones, are scarcely in keeping with the high standard of the great majority.

A commendable feature, enhancing the work as a text-book for students, is the use of heavy-face type for important phrases. The general appearance of the book, the excellence of the type employed, and the binding distinguish the production and the reputation of the publishers. B. A. T.

THE NEWER METHODS OF BLOOD AND URINE CHEMISTRY. By R. B. H. GRADWOHL, M.D., Director of the Pasteur Institute of St. Louis and the Gradwohl Biological Laboratories, St. Louis, and A. J. BLAIVAS, Assistant in the same. Pp. 240; 65 illustrations and 4 colored plates. St. Louis: C. V. Mosby Company, 1917.

THE purpose of the authors has been to collect into a compact book the larger part of the information on the subject that has appeared in the various journals during the past three or four years. This they have succeeded in doing to the advantage of the man engaged in laboratory investigation. The book is divided into three parts: (I) Technic of Blood Chemistry; (II) Chemical Analysis of Urine; (III) Blood Findings and Their Interpretation. It is well illustrated, easily read, and has both a subject and author index. On page 108 the "benzine" test for blood should read the "benzidine" test; the same error occurs in the subject index. H. E. D.

FOOD POISONING. By EDWIN OAKES JORDON, Chairman of the Department of Hygiene and Bacteriology, University of Chicago. Pp. 107; 11 illustrations. Chicago: University of Chicago Press, 1917.

IN a brief, simple, and entertaining manner the author summarizes and discusses food poisons so frequently met with in

every-day life and yet so imperfectly and indefinitely understood. He estimates 1500 to 20,000 cases of food poisonings each year in the United States. The discussion includes (1) sensitization to protein foods, (2) poisonous plants and animals, (3) mineral or organic poisons added to food, (4) food-borne pathological bacteria, (5) animal parasites, (6) poisonous products formed in food by bacteria, (7) poisons of obscure nature, (8) deficiency in some elements of foodstuffs causing disease.

It is a clear, concise summary of our present knowledge of poisoning through foods handled in a semitechnical manner, clearly demonstrating the great need of further and more thorough investigation upon foods and poisoning thereby. The book is of value to the medical profession as well as to the general public.

J. D.

PROGRESS
OF
MEDICAL SCIENCE

SURGERY

UNDER THE CHARGE OF

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The Effect of Unilateral Extraction of the Intercostal Nerves upon the Lungs and its Tuberculous Disease.—WARSTAT (*Deutsch. Ztschr. f. Chir.*, 1917, cxxxviii) performed experiments on rabbits to determine the effect of the paralyzing of the intercostal nerves on the movements of the corresponding lung. Through a longitudinal incision at the external border of the erector spinæ muscle he exposed, with local anesthesia, the first eleven intercostal nerves and divided them after separating them from the pleura. This was done distal to the giving off of the dorsal branch which supplies the back muscles. The distal portion of the intercostal nerve was removed by tearing it out, neurexairesis. The twelfth intercostal nerve was not removed because it did not innervate the respiratory muscles of the chest wall. The unilateral exclusion of breast movements by means of so paralyzing the intercostal nerves, so quieted and collapsed the corresponding lung, that it must favorably affect, if tried, a tuberculous process in the lung and promote its healing. He did a similar operation on two patients with lung tuberculosis. It is suitable for use in man because the operation is simple and secondary complications need not be feared.

The Treatment of Bony Defects of the Lower Jaw.—MCWILLIAMS (*Ann. Surg.*, 1917, lxv, 283) is convinced that no surgical lesion is generally so badly treated as infection and osteomyelitis of the inferior maxilla. This is due in the first place to timidity and ignorance on the part of the dentist who sees these patients in the beginning. His ill-advised attempts to save abscessed teeth lead to more or less wide spread necrosis of the jaw. Secondly, the general surgeon frequently attacks the necrosed area with the curet and chisel with too much vigor, thus increasing the necrosis by trauma. He reports 3 new cases and a second grafting operation on one of 2 cases previously reported. The main lessons to be learned from these patients are as follows:

Infection from the mouth at the time of making the grafts is absolutely fatal to the entire graft. A part only of the graft may necrose away. No grafting should be made in the presence of a sinus or into a granulating cavity. Grafting should be made any number of times until a successful result is obtained. In view of the great liability of bone grafts into the lower jaw to infection, McWilliams is inclined in his next cases to use costal cartilage as grafting material, since this is more viable than bony grafts and is not so liable to become infected. Absolute immobility of the lower jaw is a *sine qua non* to a successful result. Wiring the teeth proved more successful than splints. It should be maintained for three or four months after the grafting. The inlaying of the graft (always with its periosteum) into grooves cut in the sides of the fragment would seem to be a more scientific procedure than end-to-end grafting. Metal sutures had best not be used, owing to their liability to invite infection.

The Prognostic and Therapeutic Significance of Skeletal Metastases in Carcinoma of the Breast.—Levin (*Ann. Surg.*, 1917, lxv, 326) says that in the overwhelming majority of all cases of cancer of the breast the best surgical treatment do not completely eradicate the disease, but only prolong life. The correct treatment of carcinoma of the breast, complicated with skeletal metastases consists in the operative removal of the gross tumor mass combined with radium and roentgenotherapy. The radiations in a postoperative case of carcinoma of the breast should not be given only over the operative field and over the chest wall, which is the procedure generally adopted today, but should include, if not the whole skeleton, at least the spine and heads of both femurs. Moreover this combination of surgery and radiotherapy should be the method of choice in all advanced cases of carcinoma of the breast, even when there is not yet evidence of skeletal metastases. One of the important effects of radium and roentgenotherapy consists in the formation of an extensive connective-tissue stroma, surrounding and compressing the tumor cells. In skeletal metastases this stroma is transformed into bone. It is thus *a priori* self-evident that the radiotherapy must enchance the results of the attempts at cure produced by nature.

Renal Tuberculosis.—Rytina (*Ann. Surg.*, 1917, lxv, 346) reports a study of 3 cases of renal tuberculosis. The first shows that an almost generalized tuberculosis of the genito-urinary tract may be present without the production of any grave symptoms and that following radical removal of the chief foci, rapid, spontaneous retrogression of the disease in the remaining organs can take place. The second case proves the erroneousness of the teaching of some surgeons that tuberculosis of the kidney can be diagnosed by inspection and palpation of the organ at the time of operation. Indeed, bisection of the kidney from pole to pole may fail to reveal the seat of an extensive tuberculous process. This point is worthy of emphasis, as Rytina has seen, in the last few years, several cases of renal tuberculosis which showed no evidence of its existence upon the surface of the kidney, but on section and examination of its interior a most advanced tuberculous condition. The moral of this is, that the diagnosis should be made prior to operation by the

employment of the cystoscope, ureter catheterization and functional tests, and once having determined the diagnosis, its removal should be resorted to, irrespective of its normal surface appearance at the time of operation. The third case indicates that an entire kidney may be destroyed by tuberculosis and exist for years without producing any renal symptoms or change in the general physical well-being of the individual. This case also shows the advantage of kidney functional tests in surgical renal conditions and at the same time that it is not fool-proof.

The Carrel Method of Wound Sterilization.—SHERMAN (*Surg., Gynec. and Obst.*, 1917, xxiv, 255) says that if it is necessary to amputate for loss of substance, a chop or guillotine aperiosteal operation is the method of choice; this to be followed by Carrel's method of wound sterilization. According to Tuffier 80 per cent. of the amputations are due to infection and 20 per cent. to destruction of tissue. The original Dakin solution contained: 140 grams dry sodium carbonate dissoloed in 10 liters of tap water, to which 200 grams chloride of lime (chlorinated lime) is added and 40 grams boric acid. The detailed preparation is given of the solution as now used (technic of Dufresne). Many of the so-called Dakin solutions are not prepared in accordance with the formula of the name they bear and as a result the solution has been condemned where some other solution has been used in the name of Dakin. To be successful one must follow the technic of Carrel. Dakin's solution represents but 20 per cent. of the cure and the technic of Carrel represents 80 per cent. It should never be forgotten that the solution must not be heated. It should never be applied or used in the eye or intravenously, because of its hemolytic action. It should be kept in a cool place, free from exposure to light. It should never come in contact with alcohol. It has been demonstrated that the great majority of wounds can be closed by suture and without suppuration. The stay of the wounded in the hospital and period of convalescence is greatly shortened and many now leave in four to six weeks, who would have required treatment from three to six months under former method. All complications such as atrophies, ankylosis, adhesions, septicemia and amputations are minimized; the mortality rate is also greatly reduced. Sherman concludes that infection can be aborted if the treatment is begun within the first twenty-four hours. Suppuration, when well established, can be controlled if the focus can be reached. The success of the treatment is dependent upon the perfection of the Carrel technic and the acceptance of all the details. The effect of Dakin's solution is entirely local; there being no danger of toxemia from absorption, regardless of the amount used. Carrel's technic, using Dakin's solution, is a specific against infection of wounds.

The Etiology and Treatment of Varicose Ulcer of the Leg.—HOMANS (*Surg., Gynec. and Obst.*, 1917, xxiv, 300) says that in summing up the treatment of chronic leg ulcers not obviously of varicose origin, it may be said that when well defined, or of any considerable size, and presenting a hard scar base, they are best treated by radical excision and skin graft. When they are a manifestation of a previous general infection of the subcutaneous tissues (and local veins) of the lower leg

they should be conservatively treated by measures tending to improve the surface circulation. Varicose ulcers take origin in profound nutritional disturbances attributable to varicose veins, but their incidence and development are profoundly influenced by trauma and infection. Varicose ulcers arising from the familiar type of surface varix run a chronic course and are generally healed by adequate removal of varicose veins. Varicose ulcers dependent upon postphlebitic varix are characteristically different from the first class in appearance, rapid in development, always intractable to palliative treatment, generally incurable by the removal of varicose veins alone, and must be excised to be cured. The lower leg, the seat of phlebitis, must be most carefully dissected, and every means should be employed to improve, during a protracted convalescence, the circulatory conditions in the leg. Chronic ulcers originating in trauma and infection should, if well defined, be excised and grafted.

A Substitute for Joint Ligaments.—STEINMANN (*Zentralbl. f. Chir.*, 1916, xliii, 979) refers to Katzenstein's case in which he substituted for a torn tibionavicular ligament, a free, transplanted, doubled periosteal flap, and thus overcame a traumatic flat-foot. Momberg, because, of the weakness of the periosteum, substituted a strip of the fascia lata. Steinmann obtained the Katzenstein advantage of intimate adhesion of the periosteum at the site of attachment and overcame the disadvantage of the weakness of the periosteum by taking with the periosteum a thin layer of bone. A twenty-five-year-old man, in March, 1914, tore the internal lateral ligament of the right knee. In extension of the knee, the leg could be bent outward 10 to 15 degrees. The patient experienced marked laxity of the joint on certain movements. On May 19, 1916, through a longitudinal incision, he exposed the lower end of the femur, joint, and upper end of the tibia. From the upper third of the tibia, at its inner angle, a periosteum bone flap was chiselled off, about 8 cm. long, 1 cm. wide and 3 mm. thick. This was turned upward, the upper end laid under the periosteum of the internal condyle of the femur, and fixed to it by a few sutures. This turned the bony layer of the flap outward. After three weeks' fixation, movements of the knee were begun and after six weeks, the patient got up on his feet. August 3, 1914, owing to the beginning of the war, he left the hospital, with flexion of the knee of about 90 degrees. There was no effusion in the joint, and the leg could no longer be bent outward with the knee in extension. The roentgen ray showed a shadow of the bony layer in the new ligament.

Two Cases of Fracture of the Neck of the Femur in Children.—WHITBECK (*Am. Jour. Orthop. Surg.*, 1917, xv, 17) says that the principles upon which the treatment of a fracture of the femoral neck should be based are: (1) The immediate and complete reduction of the deformity, no matter of what type. (2) Effectual means of fixation, to allow union to take place. This principle is best exemplified in the abduction method of Whitman. It applies not only to complete but also to incomplete or impacted fractures, and it is important to emphasize this fact. The results of this treatment have been shown to be most satisfactory; not only has a complete, or nearly complete, ana-

tomical restoration of the break in continuity been effected, and firm union produced, but the accompanying complete functional restoration resulted. Moreover, the danger of bed-sores and hypostatic pneumonia, which cause death in so many cases treated by traction, is well met by the abduction method. The retention in plaster renders it practical to turn the patient from side to side for bathing, and raising the head and turning from side to side at intervals drains the chest.

THERAPEUTICS

UNDER THE CHARGE OF

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Modern Methods of Blood Transfusion.—LEWISOHN (*Jour. Am. Med. Assn.*, 1917, lxviii, 826) found that 0.2 per cent. instead of 1 per cent. is the percentage of sodium citrate and blood required for the safe prevention of coagulation. Such a mixture prevents coagulation of the blood outside the body for from two to three days; 5 gm. of sodium citrate can be introduced safely into an adult. Larger amounts are extremely toxic. He rarely transfuses more than 1000 c.c. of blood, which would represent 2 gm. of sodium citrate. However, even a transfusion of 1500 c.c. of blood would require only 3 gm. of sodium citrate, a perfectly safe dosage. The introduction of citrated blood causes a temporary shortening of the coagulation time of the recipient's blood. The coagulation time returns to its previous level usually in less than twenty-four hours. The author describes the technic of transfusion by the citrate method and emphasizes the importance of preliminary tests of the donor blood. The following important facts also ought to be kept in mind in connection with this question: Donors cannot be used a second time for the same patient without another test as to hemolysis and agglutination. Blood relatives (parents and children, brothers, etc.) have to be tested just as thoroughly as strangers, as their blood often is very incompatible in spite of their near blood relationship.

The Results of Treatment in Hodgkin's Disease.—YATES and BUNTING (*Jour. Am. Med. Assn.*, 1917, lxviii, 747) summarize their clinical experience in treating 63 cases of undoubted Hodgkin's disease over a period of eight years. They believe that Hodgkin's disease is due to an infection of low virulence but imitates tuberculosis and certain malignant neoplasms especially carcinoma in many details. They advocate the radical surgical extirpation of all involved tissue possible, followed immediately by intensive roentgen-ray therapy. Before resorting to radical operation it is important to determine and eliminate the portals of entry of the infection, such as diseased tonsils,

teeth, accessory sinuses, etc. It is possible by these means to reduce the danger of local recurrences and when recurrences do occur they are usually late and assume a more chronic type of lesion. If extirpation is not to be complete the authors believe it should not be attempted. They have seen hopeless dissemination follow excision for diagnosis and believe that such test excisions should be made only exceptionally. The authors have found the use of an immune serum is distinct value although they cannot offer proof that the diphtheroid bacillus described by them is the actual cause of the disease. Patients who tolerate the serum seem to improve more rapidly and to receive more permanent benefit than those not receiving serum treatment. Arsenic is without specific and lasting value in any form yet available from Fowler's solution to salvarsan. Fresh air, sunshine and proper feeding are infinitely superior to any drugs when there is indication for tonics. With regard to results the authors conservatively decline to give exact figures but they believe that as their experience increases and methods of treatment improve greater benefits are being obtained. They are of the opinion that in about 20 per cent. of all cases recovery is a possibility. By recovery is meant freedom of signs and symptoms of the disease for a period of five years. Earlier diagnosis and the recognition that Hodgkin's disease, if treated promptly and radically, is curable would raise this percentage materially.

The Treatment of Hodgkin's Disease.—Holding and Brown (*Jour. Am. Med. Assn.*, 1917, lxviii, 701) report 18 cases of Hodgkin's disease in which the diagnosis was established by microscopic examination. These cases were all fully developed with lesions generalized throughout the body. The claims of a specific diphtheroid organism have not been proved, in fact, have been disproved by Lorrey, yet their study seems to point to an infectious origin of the disease. The treatment of Hodgkin's disease is extremely unsatisfactory both in results obtained and methods employed. Perhaps this is to be expected in a disease, the cause of which is unknown, and which on microscopic examination of involved tissues in its early stages is extremely difficult to differentiate from lymphosarcoma, lymphoma, thymoma, and the other adenopathies of lymphoid origin. No specific or constitutional method of treatment has been established. The modern methods advised are essentially the same as those employed for malignant tumors, complete excision and diagnosis by microscopic section in the earliest stages while the lesion is restricted to a single locus followed by prophylactic roentgen treatment, together with the searching out and the elimination of all possible foci of infection. The authors feel that particular emphasis should be laid on the necessity of extensive general roentgen treatment in all of these cases immediately after the diagnosis is established. The surgical removal is only local in its action, and constitutes more or less of a shock and drain on the patients' vital resources. The roentgen rays should be given over all lymphatic structures of the body, including the mediastinal and abdominal lymph nodes, thus giving us a general action which in proper dosages they have invariably found to improve the patient's general physical condition instead of weakening him as the extensive surgical operations did in the fully developed stages of the disease.

It was noticeable that better results were obtained when treatment was instituted in the early stages of the disease, when lesions were confined to one side of the neck. It is quite probable that if patients in whom the lesion was confined to the tonsil or to a few glands of the neck presented themselves for treatment, they might be cured by complete tonsillectomy and excision followed by postoperative roentgen treatment; certainly these methods should be given a thorough trial in cases in the incipient stages of the disease. The authors are of the opinion that radium will produce fully as good results as the roentgen rays in Hodgkin's disease. The results obtained by various methods of treatment over a period of three years' observation are summarized. The authors note that of the thousands of patients treated there are only two authentic cases in which the patients are reported symptom-free after five years.

The Diagnosis and Serum Treatment of Anterior Poliomyelitis.—ZINGHER (*Jour. Am. Med. Assn.*, 1917, lxviii, 817) gives a summary of cases of poliomyelitis treated with immune and normal human serum. It is interesting to see that of 54 preparalytic cases treated with immune serum, 44 remained free from paralysis, while of the 10 who developed some form of paralysis, 5 made a complete final recovery. The results with normal serum seem to be very favorable, but the number of cases treated in the preparalytic stage of the disease is too small, and a larger series of cases should first be treated before final deductions are made. The author says it is difficult to state how many of the patients treated with serum would have remained free from paralysis without serum treatment. It seemed, however, that the action of serum in poliomyelitis is beneficial; that the use of serum from recent immune donors is preferable to normal serum, but that human serum is indicated in the treatment of the acute stages, especially in the preparalytic period of the disease. When carefully observed and controlled, the treatment is harmless. A distinct reaction follows in some of the cases after the first dose; the reaction is less marked after the second, and little, if any, is noted after the third injection of serum. Two groups of cases seemed to give an unfavorable prognosis even in the earlier stages of the disease. One was the fulminating bulbar type with a rapidly progressive involvement of the respiratory center. The second type was a rapidly developing spinal paralytic form. In the latter cases, which were treated after the paralysis had already made a distinct headway and was beginning to involve the muscles of respiration, the serum showed possibly in a certain proportion of cases an inhibitory effect on further progress, which resulted in a saving of life. It is difficult to forecast, however, what the natural result of the disease would have been in these cases. Control patients without serum, in whom the muscles of respiration were involved at the time the patients came under observation, have also recovered. It seemed, however, that a larger number of serum-treated patients of the same degree of severity had remained alive than would have without the use of serum. No very definite judgment of the value of serum can be based on the results obtained in these cases. Yet, as a possible life-saving procedure, the author would continue to use the serum even in these cases and in the course of time obtain more definite

results. In his conclusions the author states that the injection of immune and of normal human serum into the spinal canal during the acute febrile stage of poliomyelitis causes a distinct cellular reaction which is mostly polynuclear in type. The phagocytic action of these cells is beneficial in poliomyelitis. Such action is enhanced in immune serum by the presence of specific antibodies. It is preferable to use fresh serum, or serum which has been obtained under sterile precautions, passed through a Birkefeld filter and bottled without the addition of a preservative. The presence of a preservative and of hemoglobin in serum enhances its irritating effect, and gives rise to the more severe types of reaction. For purposes of treatment, it is important to diagnose the cases during the preparalytic stage of the disease by the typical group of early symptoms and the changes in the spinal fluid.

A Note on Sublingual Medication.—COOPER (*The Practitioner*, 1916, xcvii, 493) endorses the sublingual administration of hypodermic tablets in many cases where hypodermic medication seems inevitable, as in cases of severe vomiting, coma, esophageal obstruction, etc. The great advantage of the method is that it does not require any apparatus nor sterilization. He believes that this method has proved very effectual and is practically as prompt in action as when the remedies are used hypodermically.

The Treatment of Certain Diseases of the Skin by the Intravenous Injection of Foreign Protein.—ENGMAN and MCGOERY (*Jour. Am. Med. Assn.*, 1916, lxvii, 1741) report the treatment of several forms of skin disease with the parenteral injection of foreign protein. The protein was obtained by using suspensions of typhoid organisms. The results were very favorable in such conditions as lupus, erythematosis, psoriasis, and several other types of dermatosis. Although the immediate results were satisfactory the treatment was often followed by relapse. They do not recommend this treatment for general use as yet but believe that its results are worthy of much further investigation.

The Diagnosis and Treatment of Hookworm Disease.—BILLINGS and HICKLEY (*Jour. Am. Med. Assn.*, 1916, lxvii, 1908) say that thymol is the anthelmintic almost universally administered throughout the United States in the treatment of hookworm disease, and it was used exclusively in their hospital until one year ago, when oil of chenopodium was substituted. Since that time, owing to the encouraging results obtained, oil of chenopodium has been adopted as the regulation treatment to the exclusion of all others, the oil being of the variety known as the Baltimore oil. Compared with thymol, oil of chenopodium gives markedly better end-results, and its value is further enhanced by the facts that not only is it followed by fewer disagreeable after-effects but with its use no dietetic precautions need be exercised either before or during its administration. The routine course of treatments for adults is as follows: Preparatory treatment: At 7 A.M. magnesium sulphate, saturated solution 60 c.c. At 7 P.M., sodium sulphate, saturated solu-

tion 90 c.c. The next morning beginning at seven, oil of chenopodium is given in doses of fifteen drops (not minims), every two hours for three doses, followed by 18 c.c. of castor oil and 2 c.c. of chloroform two hours after the last dose of chenopodium. A second dose of 30 c.c. of castor oil is given a half-hour later. Chloroform seems to have a marked synergistic action, as giving chenopodium and omitting chloroform from the castor oil has been tried but with inferior results. The authors believe that the oil of chenopodium is absolutely safe when given as directed, with the additional value that it expels not only the hookworm but also the roundworm, whipworm, tapeworm and the intestinal flukes.

The Treatment of Trichinosis with Thymol.—Booth, Goehring, and Kohn (*Jour. Am. Med. Assn.*, 1916, lxvii, 2000) state that the oral administration of thymol has been advocated for the treatment of trichinosis when the parasite is within the lumen of the intestine, but cases are seldom seen or diagnosed before lodgment of the parasites within the muscles and tissues of the body. It is futile to give thymol by mouth after the parasite has lodged itself in the muscle since the drug, after its absorption from the intestine, has its antiparasitic powers neutralized by the liver. Parenteral injections of thymol would exclude the conjugating action of the liver cells and a large percentage of the drug would be absorbed in the blood and would be carried to the muscles to attack the parasite *in situ*. They made use of a solution of 50 grains of thymol in 50 c.c. of sterile olive oil, which had been autoclaved for several minutes. The solution was then resterilized and the patient was given from 2 to 3 c.c. of this solution subcutaneously or intramuscularly daily for seven days. The administration was then discontinued for several days and then again repeated. It was noticed that following the administration of thymol oil solution there was an increase in the percentage of the eosinophile leukocytes up to 30, 45 and as high as 55 per cent. This was no doubt due to the destruction of the parasite and the absorption of the parasite protein into the blood. There was no discomfort to the patient, except that a rash appeared on the palmar surfaces of the hands which cleared up when the administration of thymol was stopped.

Tonsillectomy during the Course of Rheumatic Fever.—Norris (*Jour. Lab. and Clin. Med.*, 1916, ii, 168) reviews the literature dealing with the close relationship between tonsillitis and acute rheumatic fever, and especially with the effects of tonsillectomy as a therapeutic procedure. The general tendency has been to refrain from operating on tonsils acutely inflamed, especially when they are associated with acute joint involvement. The author deprecates this tendency and believes that there may be greater danger in deferring operation too late. If the tonsils are the source of infection, their continued presence increases the danger of secondary involvement of the heart. He believes that tonsillectomy is indicated as soon as the acute tonsillar inflammation subsides irrespective of the arthritic condition. He advises the use of salicylates in large doses to relieve the acute joint pains, before operating in order to increase the comfort of the patient.

PEDIATRICS

UNDER THE CHARGE OF

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Morbidity and Mortality of Pertussis and Measles, with Particular Reference to Age.—VEEDER (*Arch. Pediat.*, May, 1917, xxxiv, No. 5) presents a collection of statistics in charts and tables, from which he summarizes as follows: "A study of the morbidity and mortality of measles and pertussis brings out certain factors. Perhaps the most important of these is that, on an average, between 9000 and 10,000 deaths from each disease take place annually in the United States. While the death-rate as a whole, and for certain diseases as tuberculosis, diphtheria, diarrhea and enteritis under two years, and typhoid fever, shows a decrease in the registration area in the past fifteen years, that for measles and pertussis has remained practically the same. Surely no disease that causes one in every hundred deaths, or that rolls up an annual toll of between nine and ten thousand lives a year is insignificant or unimportant. A second point is the age distribution of the deaths in these two conditions. Nearly 80 per cent. of the pertussis and over half of the measles deaths occur in infants. The older the child the lower the case fatality rate. The widespread impression among the laity that it is a good thing to have these common infections of childhood early and get them over with is erroneous. The longer that they can be warded off, so much less the change of fatal or damaging complications. The mortality of the first year of life is greater than the combined mortality of the rest of childhood. A part of this—birth accidents—congenital malformations, etc., may be termed fixed and is irreducible, but far the larger part is preventable to a certain extent. Somewhere between 5 and 10 per cent. of the mortality which may be lessened is due to measles and pertussis."

Infective Theory of Acute Leukemia.—WARD (*British Jour. Children's Dis.*, January to March, 1917, xiv, Nos. 157–159) reviews 1457 cases of all varieties. He says, "The theory that leukemia is due to infection seems to derive most support from the acuter cases. Such cases are not infrequently admitted to fever hospitals, sometimes because of purpura and general symptoms, and sometimes owing to a definite membrane on the throat which closely resembles that of diphtheria." He admits that as yet no infective agent has been isolated. The cases on record of congenital leukemia give no clue of any source of infection in the mother or elsewhere. As regards leukemic mothers there is nothing in the records to show that their offspring tend to be leukemic, or that the mothers of leukemic children are leukemic. Of this series there are several cases in which this condition was present in two or more individuals who were members of the same household, but these are shown to be merely coincidences. He concludes that congenital acute leukemia is not infec-

tive, but that occasionally there is apparently infection of one person from another in older children and adults. He shows by charts that leukemia has a marked preference for the male sex; that chronic myelemia shows a majority of cases between 25 and 45; chronic lymphemia between 45 and 60; acute leukemia shows a decided preference for ages below 25. He recapitulates as follows: "The evidence of the facts here dealt with is almost entirely against the infective nature of leukemia, the established facts being: (1) That there is a congenital form of leukemia, which occurs in children whose parents are not leukemic. (2) That leukemic parents have never been known to transmit the disease to the newborn child. (3) That instances in which actual infection of one person by another might seem to have occurred are very few, although not necessarily devoid of significance. (4) That in having a marked preference for a particular sex and age leukemia differs from the infective class of diseases, and resembles the metabolic diseases and cancer.

Prodromal Symptoms of Infantile Paralysis.—Wilson (*Am. Jour. Dis. Children*, June, 1917). This paper is a study of 400 cases from the wards of the Willard-Parker Hospital, New York. Dr. Wilson takes up the prominent prodromal symptoms under the following headings: fever; gastro-intestinal symptoms; respiratory symptoms; nervous symptoms; urinary system; skin. *Fever:* Fever was the most common initial symptom, being noted in 334 of the 400 cases. Only 2 per cent had no history of fever. The fastigium was reached in twenty-four to forty-eight hours. The highest temperature reached was 106°; the average, 103°; the duration of febrile curve was from one to ten days; the average duration was four days; the temperature fell by crisis or lysis. *Gastro-intestinal Symptoms:* Vomiting was noted in 67 cases as the initial symptoms; as an early symptom in 132 cases. Constipation occurred in 156 cases. Diarrhea was not a common symptom, being present in 25 cases. Abdominal pain was an initial symptom in 21 cases; an early symptom in 25. It was usually severe and persisting several days, referred to the epigastrium and in two cases simulated appendicitis. *Respiratory Symptoms:* Throat. Sore throat was an initial symptoms in 21 cases; reddened in 27 cases; follicular tonsillitis in 14. On being admitted 100 cases showed injected fauces in 31; enlarged inflamed tonsils in 11; exudate in 4; mucopurulent discharge in 7. Epistaxis occurred in 2 cases initially. Coryza was noted in 17 cases. Conjunctivitis was noted in 9 cases. Cough was slight in 38 cases; in 2 it was severe. *Nervous Symptoms:* Drowsiness was early and characteristic in 288, or 72 per cent., varying from apathy to stupor in 47 cases. Irritability was present in 153 cases. This was associated with marked hyperesthesia in 97 cases. Tenderness and stiffness of the neck was an early and common symptom in 161 patients. Retraction of the neck and flexion of the lower extremities occurred in 40. Pain was seen in 130 cases, usually to neck, extremities, back and shoulders and chest. Tremor was present in 110 cases. Twitching was observed in 64 cases, sometimes choreiform in character. Twitching of the corner of the mouth sometimes preceded facial paralysis. Headache was noted in 78 cases; frontal or general headache was the first symptom in 12 cases. Convulsions was seen in 6 cases. Irritability in 3 cases. Delirium in 10.

Urinary System: 27 gave the history of urinary disturbance, usually a mild retention. Skin: Profuse sweating occurred in 45 cases. Rash: Red blotches in 2 cases; general erythema, 4 cases; macular, resembling measles, 8; urticaria, 4; pustular, 2; herpes, 7. Dr. Wilson notes in conclusion: "The prodromal period has been found to be the most important stage in the course of the disease, both as to early quarantine and treatment. A careful history while not diagnostic, is very suggestive particularly in an epidemic."

Occlusion of the Aqueduct of Silvius in Relation to Internal Hydrocephalus.—SCHLAPP and GERE (*Am. Jour. Pediat.*, June, 1917, xiii, No. 6). Eight cases are reported, all showing either complete occlusion of the aqueductus cerebri or obliteration of the fourth ventricle by severe pathological changes in the ependymal or subependymal tissue. "Those cases, also, developing acutely in previously healthy adults and older children, and which have shown microscopically the same pathologic changes, may have been brought about in the same manner, namely, through the stimulation by some chemical poisoning of a tissue which is embryologically defective. These cases, no doubt, differ etiologically from that large group following meningitis, the acute infectious diseases and those due to bacterial invasion of the brain substance and ependyma from extension of suppurative processes of the middle ear or of cells of the mastoid. A consideration of the life processes of the cell offers an explanation of the occurrence of many cases of congenital and acquired closure of the Sylvian aqueduct. Metabolism is nowhere more delicately expressed than in the highly complex chemical reactions of the cells of the central nervous system; and while knowledge of these reactions is still far from complete, it is, nevertheless, conceivable that any slight noxious influence may be sufficient seriously to disturb the latent forces of the glia cells, resulting in the dominating influence of one or the other of the processes residing in these cells. These life processes may be divided into the nutritive, the formative, and the functional activities. In the first, which involves an appropriation of nutritive substances from the blood, potential energy is stored up and is subsequently translated into formative or functional activity, as represented by cell division, on the one hand, or by functionation of the specialized cell, on the other. In cells which have become highly specialized, as the nerve cell, gland cell and muscle cell, the potential energy of the cell body is converted into the predominating activity, and the formative process is held in abeyance, and, so long as the normal relation between synthesis and catalysis is maintained, functional activity of the cell remains in a state of constancy. On the other hand, in those cells not highly specialized, as the ependymal, glia, and the connective-tissue cells, formative activity is easily awakened, and so it happens that in many cases of hydrocephalus, stimulation of these cells by some irritating substance results in an active proliferative process which involves not only the ependyma but the subependymal tissues of the aqueduct of Sylvius, as seen in the obliterative glioses (in these cases). The exact nature, source and means of access of such damaging stimuli are not always readily determined, and, barring the possible influence of syphilis and bacterial invasion of the meninges, ependyma and choroid plexuses, there remains to be studied more

closely the casual effects of circulating toxic by-products of fetal or maternal metabolism, and variation in function of the endocrine glands. Syphilis has not operated as a known etiological factor in this sequence, with the exception of Case 6, in which Spirocheta pallida have been found in the cerebral tissue. The Levaditi method has failed to show the presence of spirochetes in two other cases (2 and 7) which it was thought might be explained on the grounds of a luetic infection. The clinical records do not include reports of the Wassermann reaction of the blood or spinal fluids of the parents of these children."

OBSTETRICS

UNDER THE CHARGE OF

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Asphyxia Pallida from Placental Separation.—WELZ (*Am. Jour. Obst.*, November, 1916) reports the case of a primipara apparently near the end of pregnancy who had been taken with hemorrhage from the vagina, and uterine contractions had developed. On admission to hospital the patient was pale, with weak, rapid pulse, and no fetal sounds or movements could be recognized. The uterus was oval, relaxed and about the size of a nine months' pregnancy. On vaginal examination no placenta previa could be found. The membranes had not ruptured and there was considerable dilatation. Under ether the membranes were ruptured and bipolar version performed and the left leg of the child brought down. A fetus measuring 47 cm. in length was readily delivered in a condition of asphyxia pallida from which it was resuscitated by a lung motor. On examining the after-birth there were four distinct placentæ, the membranes traversed by numerous bloodvessels. The cord was attached to the center of the largest placenta, and the different placentæ were connected by the membranes which were unusually thick and vascular. The two larger placentæ were attached to the side of the uterus below the fundus, while the two smaller were in the lower uterine segment but were not placenta previa. The two lower had become detached causing hemorrhage.

Cholelithiasis Complicating Pregnancy.—FINKELSTONE (*Am. Jour. Obst.*, November, 1916) publishes the case of a multipara who when seen was pregnant between three and four months and who had an abortion. After this she was operated upon to repair lacerations, and following the operation had an attack of cholecystitis. It seemed to have resulted from the action of calomel given to the patient to move the bowels. From this she made a gradual recovery without operation, the roentgen ray showing adhesions around the gall-bladder. Sometime after this the patient became pregnant, refused operation, and had morphin to relieve pain. Consent was finally given to operation when

the gall-bladder was removed and found to contain 86 gall-stones of small size. The patient made a good recovery, the fistula healing in twenty-four days. Pregnancy was not interrupted and was then about seven months. The patient came into spontaneous labor later on and was delivered spontaneously of a full-term male child. Although there was extensive laceration it was repaired and she made a good recovery. Over a year afterward she reported with pain in the right epigastrium, apparently resulting from torn adhesions in the region where the gall-bladder had been. The use of a bismuth meal and roentgen ray was followed by temporary improvement after which the patient grew worse and suffered severe pain. Jaundice, vomiting of green material, and a gall-stone also occurred. There was a mass in the abdomen at the site of the gall-bladder. An operation was finally performed when the gall-bladder was found enlarged and chronic pancreatitis. The adhesions were separated and the gall-bladder removed, and the duodenum drained. A small stone was found on examination imbedded in the wall of the gall-bladder. This patient for nearly a year had marked symptoms of cholecystitis without jaundice, gray stools, or fever. A drainage of the gall-bladder at the first operation did not disturb pregnancy and large doses of morphin given for pain apparently did not affect the child.

The Clinical Significance of Double Uterus.—JONES (*Jour. Obst. and Gynec. Brit. Emp.*, June–August, 1915) reports the case of a patient brought to him in consultation in whom by examination it was found that a septum was present in the middle line of the vagina. On bimanual examination a separate cervix and uterus communicating with each could be plainly made out. The writer also reports the case of a multipara who was seen in consultation ten days after her third confinement. The lochial discharge had been profuse and for three days offensive. The temperature was above 103° F. and the patient was evidently septic. The uterine cavity had been irrigated with a solution of iodin but the patient was not much better. Examination showed the uterus much larger than normal and its upper part irregular in outline. Under an anesthetic a double uterus was found with one cervix. One uterine cavity was normal for the stage of the puerperal period, in the other there was decomposing blood clots and the membrane of an early pregnancy. This mass was removed and the cavity irrigated when the patient went on to recovery. There had evidently been twin pregnancy, one on one side of the uterus going to term, the other a blighted ovum in the other cavity. Another case is reported in which a multipara had missed two periods and thought herself pregnant. Rather copious bleeding seemed to threaten abortion. When seen in consultation the conditions were such that anesthesia was necessary for examination. Two separate cervices were found and also two uterine bodies. In one of them was apparently a normal, growing ovum, and in the other some fungoid mucous membrane. This was removed by a curet and the patient went to term. In another case the patient had previously suffered from hemorrhage from the kidneys and was seen after she had been pregnant for two months and had two fetal sacks removed by ovum forceps at about the tenth week. In spite of this the abdomen increased steadily in size and pregnancy with living child was present. On

examination a double uterus was found. In this case there must have been a triple conception. In the next case the patient had been married more than four years, had interruption of pregnancy and a severe abdominal pain with enlargement on the left side of the uterus, and was thought to have ectopic gestation in the left tube. To make the diagnosis sure the abdomen was opened when a double uterus was found with pregnancy on one side. This went on naturally and the patient had a living child in a normal labor. A case came under the observation of the writer which shows how dangerous it is to use cutting instruments in the uterus unless an accurate diagnosis has been made. A primipara was delivered of a small child but the uterus remained large and the outlines of a second fetus could be made out. There seemed to be a thick septum between the two halves of the uterus or a very thick bag of water. Failing to rupture this with the finger the attending physician introduced a pair of long scissors into the uterine cavity and endeavored to cut the way into the fetal sack. Very severe hemorrhage came on which was checked but returned on the next day. The patient became infected and died on the fifth day from sepsis. At autopsy there was a double uterus and a fetus in the second uterine cavity and a ragged wound in the septum between the two bodies. Large branches of the uterine artery had been cut by the scissors. The tendency of this abnormality to interfere with labor is illustrated by the case of a multipara who previously had breech presentation with the birth of dead children. In a third confinement there were found two separate uteri and two separate cervices. Labor went on until the child descended when there was delay because the second uterus seemed to hinder expulsion and manual assistance was required. In the fourth labor this was repeated but pregnancy was in the anterior uterus and the posterior was drawn up above the level of the pelvic brim and occasioned no trouble. Involution was delayed but otherwise the patient made an uninterrupted recovery. A case is reported which illustrates the difficulty in diagnosis between a fibroid tumor in the uterus and pregnancy in a double uterus. The patient had three pregnancies and when four and a half months advanced was seen because she had intermittent hemorrhage. On examination the uterus was half-way to the umbilicus, somewhat flabby with an indefinite swelling on the left side of the uterine body. The outline of the upper border of the uterus showed a deep indentation and on the left side the tissues seemed more dense than on the right. The cervix was deeply split bilaterally and the endometrium thickened. The condition present suggested placenta previa or a sponge endometrium. It was thought that the mass on the left side of the uterus was a small fibroid although the possibility of double uterus was suggested. At seven and a half months the patient expelled a dead child. The placenta was removed by hand when it was easy to ascertain that the case was one of double uterus with pregnancy in the right body. That Cesarean section may be required in these cases is shown by a case who had two Cesarean sections before the one under consideration. At the last operation the operator had endeavored to sterilize the patient by removing the Fallopian tubes. The right tube was found and removed but the left could not be discovered, and pregnancy later supervened. At operation the anterior wall of the uterus was extremely thin at the

site of a former incision. When the uterus was opened the placenta was found in front and quickly delivered. The uterus was removed to sterilize the patient when the right half of a double uterus about the size of a goose egg was found behind a fold of the peritoneum extending from the posterior surface of the bladder to the rectum. A supravaginal hysterectomy was performed followed by recovery. The next patient had a very tender abdomen with a lump in the right side extending above the umbilicus. Examination was difficult because of pain, and the abdomen was opened under anesthesia for the removal of a tumor. The tumor was rising out of the pelvis with the bowel adhesive to it, and the great oventum attached to the tumor was darkly blood stained. The mass was a bicornuate uterus, the left side larger than the right. The left tube was filled with sterile fluid; adhesions were separated and a large clot removed from the peritoneal cavity. The left tube and ovary were removed and the abdomen closed; with the patient in the lithotomy position a large swelling could be demonstrated on the left side of the vagina. This was incised and retained blood washed out. It was then discovered that the patient had double uterus and vagina. Some months afterward the patient was readmitted complaining of pain. On this occasion, under anesthesia, vaginal examination showed that there was a septum between the two halves of the vagina and also a double uterus. The divided septum between the two vaginas was excised, followed by the complete recovery of the patient.

The Presence of Bacteria in the Vagina in the Latter Months of Pregnancy.—PERMAR (*Am. Jour. Obst.*, April, 1917) has studied 130 cases to ascertain what germs are present in the vagina in the latter months of pregnancy. Among these patients streptococci were never seen as such in direct smear, and by culture only 26 strains were recovered. Only 3 of these gave the carbohydrate reactions, and as animal inoculations were not carried out, the virulence of these strains was not known. In these investigations a variety of organisms were found. A relation apparently exists between the ability of various growths to flourish in an acid medium, and the presence of these organisms, notably the streptococci, the colon bacilli and other forms, in the vagina. The presence of streptococci giving the carbohydrate reaction is comparable to that recognized in other cavities of the body in which virulent or apparently virulent organisms are constantly present without causing active disease.

Bacteria in the Newborn Causing Septic Infection.—HYMANSON and HERTZ (*Am. Jour. Obst.*, April, 1917) have examined 42 newborn infants to determine the presence of bacteria in the cavities of the body. Of the 42 cases tabulated, the results were positive in 16, and negative in 26. In only 4 cases were the same organisms found in the body of the mother. In connection with the observation of others who studied this question, there is little evidence of infection of the infant's mouth on the first day after its birth, but on subsequent days infected bacteria grow and flourish and staphylococci predominates. It is not difficult to understand how such infection can occur in view of the presence of bacteria in the mother's birth canal and the frequent manipulation of the child's mouth in cleansing before and after nursing.

GYNECOLOGY

UNDER THE CHARGE OF

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Cystitis, with Special Reference to its Localization.—In a general review of our present knowledge of the bacteriology of cystitis, GERAGHTY (*Surg., Gynec. and Obst.*, 1917, xxiv, 655) says that while all the pyogenic bacteria are capable of producing inflammations of the bladder, and most of the known forms of bacteria have been isolated by investigators at one time or another, organisms of the colon group are the most frequent cause of cystitis, both acute and chronic. Bacteriological studies have further shown the old idea to be no longer tenable that an acid cystitis is usually due to the tubercle bacillus, for as a matter of fact, the urine in the vast majority of cases in simple cystitis is acid. The colon bacillus, the staphylococcus, different varieties of the streptococcus, the gonococcus, and many other organisms are usually associated with an acid cystitis, while organisms belonging to the proteus group usually produce an alkaline cystitis, with the well-known ammoniacal, ropy, mucoid condition of the urine. It is of interest to note, says the author, that there is a peculiar specificity displayed by different bacteria for different parts of the urinary tract. Thus, the primary focus of tuberculosis in the urinary tract is well known to be practically always in the kidney, vesical tuberculosis being secondary to the infection above, when it occurs. The gonococcus has a special predilection for the mucosa of the urethra; the only portion of the bladder commonly involved is the trigone, diffuse gonorrheal cystitis being extremely rare, while proven cases of gonorrheal infection of the kidney are rarer still. The typhoid bacillus, on the other hand, attacks principally the kidney, and usually produces a lesion of mild degree, resulting in nothing more than a bacilluria. The colon bacillus, staphylococcus, streptococcus, pyocyaneus, and some other organisms attack the kidney, bladder, and posterior urethra apparently with equal facility. With the possible exception of the tubercle bacillus, there is nothing characteristic in the lesions produced by these various bacteria, and it is impossible from the symptoms or pathology of a vesical lesion to determine the variety of invading organism, but so far as therapy is concerned, a knowledge of the organism concerned is of little real value, since no special drugs have as yet been shown to have any specificity of action for any special group of bacteria. With regard to treatment, Geraghty advises in acute cystitis the liberal employment of sedatives, in order to place the bladder at rest as much as possible. To aid in this, the amount of water ingested should be decreased to the absolute needs of the individual, so that the bladder will not be compelled to be constantly expelling the rapidly accumulating urine. To combat the increased acidity of the resulting concentrated urine, alkalies should be given to the point where the reaction becomes alkaline. Urotropin is useless, in the author's opinion, in these cases, since if the

urine is allowed to remain acid the fomaldehyde liberated only adds to the irritation, while if it is rendered alkaline, the urotropin is inert. Active treatment, such as instrumentation, irrigations, and instillations during the acute stage are usually more harmful than beneficial. If the symptoms do not rapidly subside, or the condition has become chronic, it is usually an indication that there is present some complication, either in the bladder itself or elsewhere in the urinary tract, whose discovery and elimination is of the utmost importance, since in most cases the successful treatment of a case of chronic cystitis will depend upon the ability of the physician to locate the intravesical or extravesical factor which is responsible for the continuance of the infection. In a certain number of cases, however, it must be admitted that the failure of the vesical infection to disappear spontaneously is not due to any extravesical factor. In most of these, the disease is not a diffuse cystitis, but is a localized affair, with normal mucous membrane lying between the infected areas, which latter may be single or multiple. Sometimes the lesion is a localized area of reddening and hyperemia, at others there is edema of the mucous membrane, and even the formation of bullæ and superficial ulcerations. When the lesion involves only the mucosa and to a slight extent the submucosa, simple irrigations with silver nitrate, or other silver salts, with overdistention of the bladder at each treatment, will generally suffice. If the involvement extends deeper into the bladder wall, however, such irrigations have but little effect. Here Geraghty fills the bladder with salt solution, and then through a ureteral catheter cut off square at the end, with no side eye, he injects directly against the infected area a 10 to 20 per cent. silver nitrate solution, which being instantly neutralized by the salt solution, does not irritate the remainder of the bladder mucosa. In some cases, there is found on cystoscopic examination a localized area in which the mucosa looks whiter than normal, with a puckered or scarred condition. Here one can feel reasonably sure that the condition involves the whole thickness of the bladder wall, and that no local applications will afford relief, but that extensive resection must be resorted to. These are the cases which have been especially studied by Hunner, whose work was reviewed in this department about two years ago.

Peritonitis following Acute Ovaritis of Anginal Origin.—According to WILDER (*Tr. Chicago Path. Soc.*, 1916, x, 46) hemogenic disease of the ovaries, arising by metastasis from disease of the tonsils or other distant foci, is probably more common than is usually supposed, and may account for many obscure cases of peritonitis. The occurrence of ovaritis as a sequel of general sepsis, measles, typhoid, cholera, and other infections has been observed, but the instances recorded are few, and the general tendency of gynecologists is to consider ovarian disease as a gonorrheal infection, ascending from the lower genital tract. It is significant, however, that of all reported cases of so-called primary peritonitis, a decided majority have occurred in females, this predilection suggesting to the author the possibility that the sex organs play a significant role. Most of these cases occurred during the course of a tonsillar infection, and it seems more than probable that they were in reality metastatic infections from the throat. The following case in support of this theory is reported by Wilder: The patient was a child,

aged six years, who was seized with an attack of apparently ordinary tonsillitis. She complained of sore throat, and had a temperature of 103°, with large, edematous hyperemic tonsils, studded with white patches. The cervical and submaxillary lymph nodes were enlarged and tender. On the third day, when the throat condition was apparently improving, the child suddenly became acutely ill with symptoms of peritonitis. Immediate operation showed the peritoneum to be hyperemic and lusterless, with a small amount of thin pus in the pelvis. In spite of drainage the patient died in forty-eight hours, and autopsy showed an intense pelvic peritonitis, with much less involvement of the upper abdomen. There were no perforations, volvulus, or other demonstrable cause. The appendix was slightly hyperemic, but otherwise normal. The pelvic organs were all hyperemic, but the ovaries showed in addition some hemorrhages, and a few diplococci and short chain streptococci in the ovarian tissue. Cultures from the abdominal fluid at operation showed a pure growth of Gram-positive diplococci and short chain streptococci. Three quite similar cases from the literature are quoted by the author, who believes that these have all been cases of acute peritonitis, secondary to an ovarian metastasis from the throat infection.

Surgical Treatment of Benign Vesical Neoplasms.—The universally recognized treatment today for non-malignant intravesical growths—papillomata—is of course fulguration. As BEER (*Surg., Gynec. and Obst.*, 1917, xxiv, 646) points out, however, there are a few cases in which this method of treatment is not applicable. These fall under the following heads: (1) Patients that are intolerant to cystoscopy. With local anesthesia and morphin most of these can be overcome. (2) Patients that bleed furiously at every introduction of the cystoscope, so that no view can be obtained. (3) Patients whose tumors are so placed that they cannot be reached. (4) Patients suffering from papillomatosis of the bladder, either primary or following a surgical operation for papilloma, which operation has implanted many growths all over the bladder wall. For the small number of cases comprised in these groups, some form of cutting operation becomes necessary, but for the older method Beer substitutes an entirely new technic in order to safeguard the patient from the recurrences which almost invariably occur in the ordinary cystotomy performed for the removal of a papilloma. In Beer's method the intravesical operation is done entirely with the Paquelin (hooked point) cautery: the bladder is not filled with fluid before opening it; the incision in the bladder is gradually enlarged without any sponging or rough handling, and each tumor as it presents is burned to a crisp; every suspicious spot in the bladder is cauterized, and the edges of the bladder incision are similarly treated. Finally the whole operative field is soaked in alcohol to destroy any particles of viable growth that might have accidentally broken off during the manipulations. In order to get an adequate exposure the patient is placed in the Trendelenburg position and the bladder drawn out of the abdomen by its urachal end, this technic allowing the peritoneum to be stripped back without bruising the bladder or its contained growths.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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Types of Lesions in Chronic Passive Congestion of the Liver.—These lesions have been described by a variety of terms of which the name nutmeg liver has been in most common use. It has, however, been pointed out by not a few investigators that the character observed in passive congestion of the liver giving it the nutmeg appearance, was not uniformly the same. Moreover, there has been of late years a considerable discussion concerning the question of the important factors which brought about the tissue changes found in passive congestion of different grades. To a great degree, the original contention that the damage of the liver columns in the central portions of the lobule was the result of unusual venous pressure, has now been dropped. LAMBERT and ALLISON (*Johns Hopkins Hospital Bulletin*, 1916, xxvii, 350) have again reviewed the subject in a study of 112 cases of well marked chronic passive congestion coming to autopsy. In the majority of these cases the hepatic stasis was the result of a cardiac or vascular lesion. The liver is commonly heavier than normal, the increased weight being in part due to the excess blood present in the organ. A considerable difference in weight may be found in the same liver when weighed immediately after removal and when weighed again sometime later. The appearance of the cut liver varied with the duration of the circulatory disturbance, and, although some common features could be recognized in all specimens, yet a close analysis readily distinguished types permitting of a classification. An interesting point made by these authors is that under the conditions of these hepatic lesions the liver demonstrates a poor ability for regeneration. And, furthermore, regeneration was not most active in the specimens from young individuals but was rather associated with the chronic lesions in middle age or elderly individuals. This is probably due to the fact that examples of chronic congestion are found more often in old people; whereas in the young the acute stage of the same process is found prior to the period of regeneration. These authors have found five distinct types of lesion in passive congestion of the liver. These types are to some degree at least, merely stages of one and the same process; in fact it would appear that any one of the type lesions may progress to the next grade in severity by increasing either the duration or the severity of the blood stasis. These five types are determined by microscopic

analyses and are dependent upon the grade of dilatation of the liver sinuses and the degree of atrophy or necrosis of the liver cells. The types are as follows: (1) Capillary dilatation with atrophy of central cells, found in moderate circulatory disturbances of various kinds; (2) central degeneration with or without congestion, a stage of degeneration slightly more advanced than the preceding; (3) central fat accumulation with hyperemia or necrosis, a peculiar type usually found in the young in acute rheumatic fever; (4) central necrosis usually associated with hemorrhage, the advanced nutmeg lesion described by Mallory; (5) collapse fibrosis or cardiac cirrhosis. This last condition is more apparent than real, there being little if any increase in the amount of connective tissue originally possessed by the liver. The important factors which lead to the various changes in the liver substance are blood stasis, tissue asphyxia, interstitial hemorrhage and autolysis. The actual effect of the blood-pressure upon surrounding tissues appears to be slight.

The Comparative Resistance of Bacteria and Human Tissue Cells to Certain Common Antiseptics.—LAMBERT (*Jour. Exper. Med.*, 1916, xxiv, 683) discusses some interesting experiments performed by him to determine the comparative effects of antiseptics on bacteria and tissue cells of humans. Tissue of lymph glands removed at operation or autopsy was grown in a plasma medium with Staphylococcus aureus. He used this organism because it is moderately but not highly resistant to the ordinary antiseptics. The antiseptics used were mercurials, cyanides, iodin, phenol, tricresol, argyrol, alcohol, hypochlorites and a few others. The technic was as follows, thin layers of tissue were placed in a fluid culture of staphylococcus for several minutes. They were then transferred to the disinfectant solution for one hour, then washed in isotonic salt and placed in the plasma medium. Controls of infected, non-treated tissue and non-infected tissue were made. Most of the chemicals were found to be more harmful to the tissue cells than to the bacteria; in fact, the one marked instance of the opposite result was in the test with dilute iodin ($\frac{1}{2500}$ to $\frac{1}{1500}$). It was found with this chemical, however, that application of it to fibrin caused a dissolution of the fibrin even though it did not injure the tissue cells. Alcohol was potent only in 50 per cent. solutions and had an inhibitory effect on the growth of cells in this strength, although in weaker dilutions it stimulated rather than inhibited the growth of the tissue used. The author concludes that of the many antiseptics tried, iodin is more clearly an ideal antiseptic than any of the others.

A Study of Physiological Activity of Adenomata of the Thyroid Gland, in Relation to Iodin Content as Evidenced by Feeding Experiments on Tadpoles.—Previous experimenters have shown that the feeding of dried thyroid to tadpoles causes an early differentiation of structures in proportion to the quantity fed or the percentage of the iodin content. GRAHAM (*Jour. Exper. Med.*, 1916, xxiv, 345) used this method to determine the physiological activity of adenomatous tissue of the thyroid as compared with normal thyroid substance. For the feeding experiments, human thyroid and its adenomata were used. The material was fed to tadpoles and observations were made upon their

growth from day to day. Numerous protocols are given for some of the experiments. The author found that the so-called adenomata of the thyroid possess characters which influence the development of tadpoles in a manner quite similar to that of the normal thyroid. The action appears to be dependent upon the iodin content. The results of these feeding experiments were not so simple to interpret as might appear at first sight. Discrepancies as to the time of death, appearance of forelegs, emaciation and rate of growth were not always parallel to the iodin content. Some of these discrepancies, the author believes, may be explained by accident of feeding or slight differences of age, size and susceptibility to the materials fed. The action of the thyroid depends not upon a specific stimulus to differentiation but upon a stimulation to metabolism in general, in proportion to the iodin consumed. High iodin content produces rapid emaciation, at the time resulting in differentiation even in tadpoles dying in eight to twelve days. Low iodin content results in differentiation at an earlier period than the controls. Tadpoles fed on thyroid with practically no iodin grow better than controls, the thyroid serving simply as a food. In the experiments undertaken the author points out that as the active principle of the thyroid was demonstrated in the adenomata these tumorous masses have a functional capacity.

Technic of Cultivating Human Tissues in Vitro.—Various attempts have been made to cultivate human connective tissue *in vitro* in a culture medium of a pure human plasma, but practically all have been failures, owing to the early rapid liquefaction of the fibrin. The modifications of this human plasma made by Losee and Ebeling were unsuccessful. However, by diluting the plasma with Ringer's solution, as recommended by Carrel, they were able to propagate human connective tissue cells through several subcultures, in one case as long as sixty days, by making the transfers every twenty-four to forty-eight hours. LAMBERT (*Jour. Exper. Med.*, 1916, xxiv, 367) in the cultivation of the tissues of lower animals noted that the plasma of pigeons and fowls never liquefied. He therefore prepared a mixture of a small amount of chick plasma with a considerable quantity of human serum, into which he put various human tissues obtained at operation. No liquefaction occurred and active progressive growth, with numerous mitotic figures, was seen in the majority of preparations in which soft friable tissue was used. After careful study the author found that the optimum medium consisted of 1 part fowl plasma to 4 parts human serum; growth in pure fowl plasma was possible though neither so active nor prolonged as in a mixture. The author states that transfers did not have to be made oftener than every five days, and that propagation through subcultures might be carried on for several months and *in vitro* indefinitely. In addition to experiments on culture medium the author studied the length of time that tissues may be preserved after their removal from the body. They were placed in salt solution in a Petri dish and put in an ordinary wooden ice-box whose temperature ranged from 10° to 15° C. The results of these studies showed that human connective-tissue cells and the cells of certain benign tumors remain alive in an ice-box from six to eight days, ten days probably representing the limit of survival. The optimum temperature for such preservation

was not determined. Tissues obtained at operation gave the best results, but autopsy material removed one to four hours after death sometimes showed active growth. The author, in the performance of these various experiments, also made note of the fact that the presence of normally existing iso-antibodies (agglutinins and hemolysins) in human serum was without influence on the growth of human tissues *in vitro*. In other words, human tissues are no more sensitive to variations in the culture medium than are those of the lower animals. Hence autogenous serum has no advantage in tissue culture over homologous serum.

The Classification of Streptococci.—There is no subject in the field of bacteriology of wider interest which although receiving much attention and study for practical application has still remained in a chaotic state from the stand-point of classification, than the streptococci. Many attempts have been made to classify the streptococci and not a few of them have served a useful purpose inasfar as they could be applied. Broadly, however, certain modes of classification have, up to the present, not lent themselves as being practical. This is particularly true of the immune reactions. The mode of classification has, therefore, again reverted to the adoption of a practical method based upon cultural procedure. Such a classification has been put together by HOLMAN (*Jour. Med. Res.*, 1915, xxxiv, 377). In this classification he has introduced no new media or reactions but by analyzing, in the study of a great number of streoptococci, the value of many cultures and reagents suggested by others, he has eliminated those of no practical importance and retained others having a differential value. Holman points out that for any classification of bacteria based upon cultural methods a standard procedure for the making of the media must be adopted. For the group of streptococci where special media other than those employed for the coli-typhi group are necessary, there has, up to the present, been no uniformity of technic. Holman describes clearly his procedure for the isolation, plating and differential cultivation of the streptococci. This group of microörganisms presents some difficulties not so prominent with other bacteria. One of these, which appears to have been overlooked by others, is that of obtaining pure cultures. Holman has found that when the pure strain has been obtained the cultural characters upon the differential media used are quite permanent. The streptococci which he has under discussion are non-capsulated forms. He divides the streptococci into two groups by means of blood agar. The further differentiation is accomplished by means of serum broths containing lactose, mannit, and salicin respectively. Thus under each of the two main groups, the hemolyzing and non-hemolyzing streptococci, there are developed eight distinct subgroups depending upon the fermentation or non-fermentation of the given carbohydrates. Five of the hemolytic varieties are known by definite names: S. infrequens, S. pyogens, S. anginosus, S. equi, S. subacidus. Five distinctive names have also been applied to varieties of the non-hemolytic streptococci: S. fecalis, S. mitis, S. salivarius, S. equinus, S. ignavus. The author has tested out over 1100 strains by means of this classification and he has also applied the method of classification to 2400 streptococci isolated by others. The practical application of this means

of classification has shown that the organisms found in distinct habitats remain true to form and it is often possible to suggest the source of an infection by the cultural characteristics determined by this technic. The work marks a distinct advance in our knowledge of streptococci. Those who are more particularly interested in this subject must consult the original article.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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An Epidemic Resulting from the Contamination of Ice-cream by a Typhoid Carrier.—CUMMING (*Jour. Am. Med. Assn.*, April 21, 1917, lxviii, No. 16, 1163) reports the following outbreak: Twenty-nine persons attended a country school picnic at Helm, California, May 13, 1916. That evening many of those in attendance were taken with nausea, vomiting, and diarrhea. These symptoms were of about two days' duration, and with two exceptions all those thus affected developed typhoid fever in about eight days. Twenty-three persons in all came down with the disease, 3 of whom died. It was found that all of those who were made ill had eaten chocolate ice-cream. All those who partook of this food developed typhoid fever with two exceptions, namely, Mrs. Y., who made the chocolate ice-cream, and her daughter, both of whom, however, suffered from nausea, vomiting, and diarrhea. It was found that Mrs. Y. was a typhoid carrier who had had the disease seventeen years before, and had been responsible for at least four other cases of typhoid fever in persons living in her household during the seventeen years. Her daughter escaped the disease, having had antityphoid vaccine two years previously. The outbreak is further interesting for the reason that Mrs. Y.'s blood agglutinated typhoid cultures only in dilution of 1 to 50 and then incompletely. The California State Board of Health makes an effort to keep in touch with all typhoid carriers, not only for the purpose of directing their daily pursuits along lines which will not endanger the public health, but also for the purpose of making investigations of the carrier problem. Typhoid carriers are not isolated but are required to sign an agreement to take no part in the preparation or handling of food which may be consumed by persons outside of their immediate family, nor to participate in the management of a boarding-house, restaurant, food store, or any other occupation involving the prepara-

tion or handling of food. The carriers also agree to take precautions with reference to the disposal of excreta, and to notify the local health officer in case of change of residence, and to comply with other requirements. This contract is renewed every six months. The author concludes that the typhoid history of Mrs. Y. demonstrates the inefficacy, from the standpoint of community health, of treating a case of typhoid without seeking the source of the infection. It is seventeen years since she herself had typhoid; there are many isolated cases of the disease reported among those with whom she came in contact; finally, this epidemic, traced indubitably to her, occurred. Had the first case, years ago, for which she may have been responsible, been traced to its source, the subsequent cases, the economic loss to the community, and the three deaths could have been avoided.

Detection of Hydrocyanic Acid Gas.—GRUBBS (*Public Health Reports*, April 20, 1917, p. 565) states that instructions issued to the officers of the Public Health Service on the subject of hydrocyanic gas fumigation of vessels directed that "Before declaring it safe to enter holds, a captive animal (guinea-pig, rat, cat, etc.) shall be lowered and exposed to the aërial content of such compartments, and the effect produced, if any, shall be a guide in estimating the amount of gas present." In trying to determine just what dilution of hydrocyanic acid gas should be considered dangerous to man, volunteers have breathed gas from one-half and from three-fourths ounce sodium cyanide per 1000 cubic feet for two minutes and one and one-half minutes respectively, without feeling any effect, but this has at other times caused dizziness. Grubbs believes that where work must be done and a climb is required to reach the open air a mixture of 0.024 per cent. hydrocyanic acid gas (one-half ounce sodium cyanide per 1000 cubic feet) should be considered the limit of safety. With this limitation in mind the susceptibility of small animals usually available for the purpose of testing holds was studied, and the following conclusions reached: Sparrows or other small birds are the most delicate live indicators for hydrocyanic acid gas, but are not recommended for routine work; mice or tame rats are almost as susceptible as sparrows and are probably the best test animals available; cats are sufficiently susceptible and with care the same animal may be used several times; guinea-pigs are quite resistant to the effects of the gas and should never be used where rats are available; if guinea-pigs be the only test animals obtainable, exposure should be prolonged and other allowances made for these animals' increased resistance to the gas.

Weil's Disease or Infectious Jaundice.—NOGUCHI (*Jour. Exper. Med.*, May 1, 1917, xxv, No. 5) atates that infectious jaundice has been known for a long time to occur among troops in barracks, among sewer workers, miners, and rice planters, and its clinical entity has been recognized by Larrey, Ozanam (1849), Monneret (1859), Laverau (1865), Lancerau (1882), Landouzy (1882), Mathieu (1886), and Weil (1886). Weil described 4 cases with typical symptoms, and the disease is very often called by his name. Weil's disease is characterized by sudden onset of malaise, often intense muscular pains, high

fever for several days, followed by jaundice and the appearance of bile pigments, albumin, and casts in the urine; in severe cases epistaxis, subcutaneous hemorrhages and lymphadenitis are observed. A disease supposed to be identical with Weil's disease of Europe is prevalent in Japan, and in 1914 Inada and Ido succeeded in transmitting to guinea-pigs the typical experimental disease, accompanied by jaundice, hemorrhages, albuminuria, etc., by inoculating them with blood of patients suffering from the Japanese form of infectious jaundice. In the blood and various organs of the animals they discovered a new spirochete, which they also found in the human specimens. Spirocheta icterohemorrhagiæ, as it was designated by Inada and his associates, has since been proved beyond doubt to be the causative agent of the disease in question. A year and a half later, Uhlenhuth and Fromme, and also Hubener and Reiter, showed that the Weil's disease prevalent among the German soldiers during the present war could also be transmitted to guinea-pigs by injecting them with the blood of patients. It was not until 1916, however, that Hubener and Reiter announced the finding of a spirochete in the experimental material (liver, blood, kidney, etc.), which they called Spirocheta nodosa. Following the publication in America of the article by Inada and his collaborators, Stokes and Ryle succeeded in transmitting the disease to guinea-pigs by inoculating them with the blood of British soldiers in Flanders who had Weil's disease, confirming at the same time the presence of a spirochete closely resembling the Spirocheta icterohemorrhagiæ of the Japanese workers. Stokes, Ryle and Tytler left the question of the identity of the two strains (the Belgian and the Japanese) open for future discussion. In the meanwhile, Martin and Pettit, Costa and Trosisier, Garnier and Reilly, Renaux, Merklen and Lioust, Ameuille, Salomon and Neveu, and others, working among the French soldiers on the western front, reported similar clinical and experimental findings. They also considered the spirochete isolated from the French specimens to be closely related to the Japanese strain. On the Italian front numerous cases of jaundice have been observed, and Monti has demonstrated the spirochete in the experimental material. According to MacKenzie, there were at one time a considerable number of cases of infectious jaundice among the Canadian soldiers stationed at Salonica. It is of interest to note that while the mortality among the Japanese is as high as 38 per cent., that of the European soldiers did not exceed 2 to 3 per cent. It seems reasonable to assume that the Japanese strain has already acquired a marked increase in virulence for human subjects, owing probably to a more frequent passage from man to man. Such transmission is more frequent in Japan, for example, among the rice planters and miners with imperfectly protected feet, than in Europe, where exposure to the infection was brought about only through the unsanitary conditions of war. The entrance of this spirochete into the human body seems to be of comparatively recent occurrence. The discovery of the spirochete in apparently healthy wild rats caught near the infected districts seems to support the theory that the disease was originally epizoötic among certain rodents, particularly wild rats, and after a long sojourn in this species of hosts its virulence for these animals has been reduced to such an extent as to cause the latter no

inconvenience, or, at least, a state of tolerance for the spirochete has developed. In America, especially in the United States, there have been few epidemic or endemic cases of infectious jaundice reported from various quarters of the continent (Toronto, Middle Western and Southern United States) and from Cuba, but it was not known whether or not these cases corresponded with those found in Europe and Asia. The discovery of the specific pathogenic agent now enables us to answer this question experimentally. The author collected a large number of wild rats and removed their kidneys for the purpose of ascertaining whether or not the organs contained the spirochete which causes the typical experimental lesions characteristic of the organism of infectious jaundice. By inoculating the emulsion into guinea-pigs, he has been able to produce a typical icterohemorrhagic spirochetosis altogether identical with the findings in the guinea-pigs which died of the injections of the Japanese and Belgian strains of Spirocheta interohemorrhagiæ. The strain of spirochete isolated produced death in from nine to twelve days, attended by marked jaundice, cholemia, choluria, and extensive hemorrhages in various viscera, The author concludes that wild rats captured in this country carry in their kidneys a spirochete which possesses the morphological and pathogenic properties characteristic of Spirocheta icterohemorrhagiæ discovered by Inada in the Japanese form of infectious jaundice. Cultures of the American, Belgian, and Japanese strains of the spirochete were obtained by a special technic, the first two strains having been cultivated artificially for the first time. Animals actively immunized against the Japanese strain resist inoculation, not only of the same strain, but also of the Belgian and American strains. The Belgian strain produces immunity equally effective against all three strains. Experiments to ascertain whether the immunity afforded by the American strain also protects against the Japanese and Belgian strains are in progress. These findings warrant the conclusion that the spirochetes designated as the Japanese, Belgian, and American are probably identical. On account of its distinctive features, a new genus, Leptospira, has been suggested as the designation of this organism.

Some Factors Alleged to Influence the Duration and Severity of Vaccinia.—Force and Stevens (*Jour. Am. Med. Assn.*, April 28, 1917, lxviii, No. 17, 1247) find that in the course of normal vaccinia, the maximum development occurs on the tenth day and scab separation takes place on the twentieth day after vaccination. Dyer ("The Way to Vaccinate," *Am. Jour. Trop. Dis. and Prev. Med.*, 1913, i, 425) paints the vesicles with tincture of iodin, clips the top with sterile scissors, and cauterizes the base with a 6 per cent. solution of silver nitrate. Unna ("Nawssende Ekzeme," *Berl. klin. Wchnschr.*, 1915, lii, 281) applies a mixture of 8 parts of zinc oxide ointment with 1 part each of calcium carbonate and sulphur lotum. Schamberg and Kolmer ("Treatment of the Vaccination Site with Picric Acid Solution," *Lancet*, London, 1911, ii, 1397) paint the vesicle at the end of forty-eight hours with a 5 per cent. alcoholic solution of picric acid. Force and Stevens tested these three methods and found that they did not possess any advantage so far as decreasing the redness and shortening the course of the vaccinia is concerned.

Provocative and Prophylactic Vaccination in the Vaginitis of Children.—A. F. Hess (*Am. Jour. Dis. Child.*, November, 1916, xii, 466–476) states that postmortem examinations show that in the subacute and chronic cases of vaginitis in infants, the cervix is most frequently involved and that the vagina generally shows no signs of inflammation. Cervicitis would therefore seem to be a more correct term, in this connection, than vaginitis. When numerous pus cells without bacteria are found in smears made from the cervix, an inflammation may be assumed to be present, and in the overwhelming majority of instances the inciting factor will be found to be the gonococcus. Other microörganisms may, however, be the cause of the inflammatory process, for example a streptococcus. It should be borne in mind that smears taken from newborn infants very frequently show pus cells, probably due to the invasion of the vagina by saprophytic bacteria, and that, in the newborn, they should not be considered pathological or as evidence of gonococcal inflammation. Gonorrheal vaginitis, or cervicitis, should not be regarded as a disease encountered especially in institutions, as it may be found in a considerable proportion of infants living in the crowded tenements in the city. In child caring institutions, the greatest obstacle to limiting and controlling the spread of this disease is the difficulty of recognizing latent cases. By means of provocative inoculations of gonococcus vaccine, we have found it possible to convert the concealed carrier into an open case, and in this way to discover many cases which had eluded detection. Vaccinations have also some prophylactic value, and may either confer protection or render subsequent infection of a mild character, so that it assumes a bacteriological rather than a clinical type. There is not only a natural susceptibility to this infection and an acquired susceptibility, as occurs in the course of scarlet fever, but a natural immunity, which may be sufficient to protect infants who come in contact with infected patients.

The Virulence of Diphtheria Bacilli from Diphtheria Patients and Diphtheria-carriers.—Weaver (*Jour. Infect. Dis.*, February, 1917, xx, No. 2) states that diphtheria bacilli from patients with diphtheria and from carriers who have been in contact with such patients are practically always virulent. The bacilli in such cases usually remain virulent up to the time of disappearance, even though a long time has elapsed. Carriers should be kept in isolation until the bacilli have been gotten rid of, or until the strains cultivated have been proved to be non-virulent. Cultures from the nose as well as from the throat should be made in all suspected cases.

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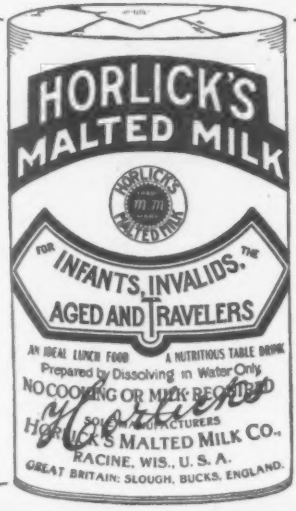
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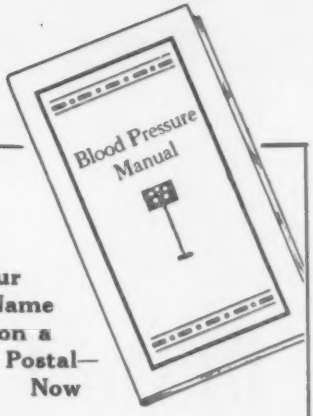

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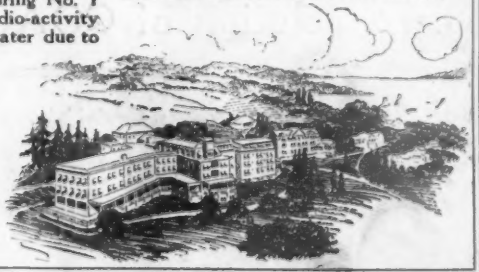
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